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MS PROVISIONAL PATENT APPLICATION
PTO/SB/16(8-00)

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C.F.R. § 1.53 (c).

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TITLE OF THE INVENTION (280 characters max)

NOVEL FUSIDIC ACID DERIVATIVES

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ENCLOSED APPLICATION PARTS *(check all that apply)*

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☒ A check or money order is enclosed to cover the Provisional filing fees.	☒ Large Entity ($160.00)
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

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Date: July 17, 2003

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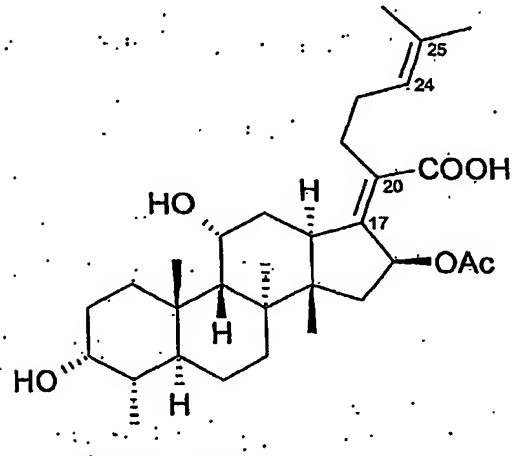
NOVEL FUSIDIC ACID DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to novel fusidic acid derivatives, to pharmaceutical compositions comprising said derivatives, as well as to their use in therapy.

BACKGROUND OF THE INVENTION

Fusidic acid belongs to the fusidanes which is a small family of naturally occurring antibiotics.



Fusidic acid

The fusidanes have in common a tetracyclic ring system with a unique chair-boat-chair conformation, which distinguishes them from steroids. Therefore, in spite of some structural similarity with steroids, namely a tetracyclic system, the fusidanes do not exert any hormonal activity. The fusidanes also have in common a carboxylic acid bearing side chain linked to the ring system at C-17 via a double bond and an acetate group linked at C-16. Fusidic acid, a fermentation product of *Fusidium coccineum*, is the most antibiotically active compound of the fusidanes and is the only fusidane used clinically in treatment of infectious diseases. Fusidic acid (Fucidin®) is used clinically for the treatment of severe staphylococcal infections, particularly in bone and joint infections, in both the acute and the intractable form of the disease (*The Use of Antibiotics*, 5th Ed., A. Kucers and N.McK. Bennett (Eds.), Butterworth 1997, pp. 580-587, and references cited therein). Although fusidic acid is most commonly used against staphylococci, it is also used against several other gram-positive species. The clinical value of fusidic acid is also due to its efficient distribution in various

tissues, low degree of toxicity and allergic reactions and the absence cross-resistance with other clinically used antibiotics. Fusidic acid is widely used in local therapy for a number of skin and eye infections caused by staphylococci. It is generally given in combination with common antibiotics such as penicillins, erythromycins or clindamycin. It has also been used as an alternative to vancomycin for the control of *Clostridium difficile*. Compared to staphylococci, several other gram-positive cocci are often less susceptible to fusidic acid. As an example, streptococcal species are generally up to 100-fold less sensitive to fusidic acid than staphylococci [Kuchers et al; *supra*]. Other sensitive bacteria include gram-positive anaerobic cocci, such as *Peptococcus* and *Peptostreptococcus spp.*, aerobic or anaerobic gram-positive bacteria, such as *Corynebacterium diphtheriae*, *Clostridium tetani*, *Clostridium difficile* and *Clostridium perfringens*. Gram-negative bacteria are resistant except for *Neisseria spp.* and *Legionella pneumophila*. The drug is highly potent against both intracellular and extracellular *M. leprae*. The structure-activity relationship (SAR) of fusidic acid has been extensively studied and a large number of analogues have been prepared. However, only a few of these analogues have shown activities comparable with that of fusidic acid. In spite of the extensive SAR studies, the potential of side chain modifications has not extensively been explored.

Compared to other antibiotics, fusidic acid has so far not developed serious clinical problems with drug resistance [Turnidge, *Int. J. Antimicro. Agents*, 12, S35-S44, 1999]. However, as discussed above the substance in itself has a fairly limited antibiotic spectrum, and it might therefore be desirable to develop novel analogues based on fusidic acid with an antibiotic activity against a broader range of pathogenic microorganisms, and in particular streptococci.

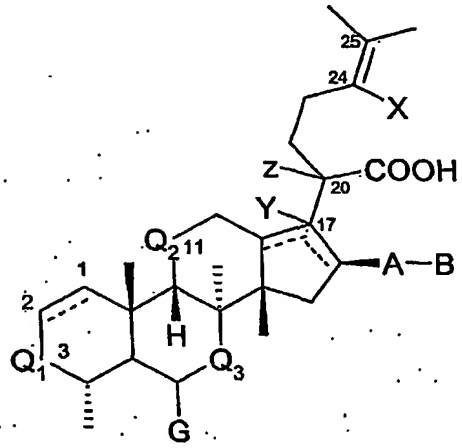
Attempts to improve the therapeutic properties of fusidanes by manipulating the side chain have previously been made. Thus, WO 02/070537 discloses fusidic acid derivatives wherein the C17-C20 double bond has been converted to a cyclopropane moiety by introduction of a methylene group.

WO 01/29061 discloses fusidic acid derivatives wherein the C17-C20 double bond has been saturated.

SUMMARY OF THE INVENTION

The present inventors have surprisingly found that fusidic acid derivatives wherein C-24 is substituted retain the activity against staphylococci and significantly increase the activity

against streptococci. Accordingly, the present invention relates to compounds of general formula I



[I]

wherein X represents halogen, trifluoromethyl, cyano, azido, alkyl, alkenyl or aryl, wherein said aryl may optionally be substituted by alkyl, alkenyl, halogen, azido, trifluoromethyl or cyano;

Y and Z both represent hydrogen, or together with the C-17/C-20 bond form a double bond between C-17 and C-20, or together are methylene and form a cyclopropane ring in combination with C-17 and C-20;

A represents a bond, O, S or S(O);

B represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} acyl, C_{3-7} cycloalkylcarbonyl or benzoyl, all of which are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, alkoxy and azido, or, if A represents a bond, B may also represent hydrogen;

Q_1 and Q_2 independently represent $-CH_2-$, -C(O)-, -(CHOH)-, -(CHOR)-, -(CHSH)-, -(NH)-, $-(CHNH_2)-$ or -(CW)-, wherein R represents C_{1-6} alkyl and W represents halogen, cyano, azido or trifluoromethyl;

Q_3 represents $-CH_2-$, -C(O)- or -CHOH-;

G represents H, OH or $O-CO-CH_3$;

two bonds in the pentacyclic ring being shown with full and dotted lines to indicate that either of the two bonds may be a double bond, in which case Y is absent and Z represents hydrogen;

the bond between C-1 and C-2 being either a single or a double bond;

and pharmaceutically acceptable salts and easily hydrolysable esters thereof.

In another aspect, the invention relates to compounds of formula I for use in therapy, and in particular to pharmaceutical composition comprising a compound according to formula I together with a pharmaceutically acceptable excipient or vehicle.

In a further aspect, the invention relates to a method of treating infections, the method comprising administering an effective amount of a compound according to formula I to a patient in need thereof.

In a still further aspect, the invention relates to the use of compounds according to formula I for the manufacture of a medicament for the prevention or treatment of infections.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

In the present context, the term "alkyl" is intended to indicate a univalent radical derived from an alkane by removal of a hydrogen atom from any carbon atom, and includes the subclasses of primary, secondary and tertiary alkyl groups, including for example C_1-C_{12} alkyl, such as C_1-C_8 alkyl, such as C_1-C_6 alkyl, such as C_1-C_4 alkyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, hexyl, nonyl, dodecanyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl and cyclohexyl. Alkane refers to an acyclic or cyclic, branched or unbranched saturated hydrocarbon and therefore consisting entirely of hydrogen atoms and carbon atoms.

The term "alkenyl" is intended to indicate to a straight or branched acyclic hydrocarbon having one or more carbon-carbon double bonds of either E or Z stereochemistry where applicable. The term includes, for example, C_2-C_{12} alkenyl, C_2-C_8 alkenyl, C_2-C_6 alkenyl, vinyl, allyl, 1-butenyl, 2-butenyl, and 2-methyl-2-propenyl.

The term "acyl" is inteded to indicate a radical of the formula –CO-R, wherein R is alkyl as defined above, for example C_1-C_6 acyl.

The term "alkoxy" is intended to indicate a radical of the formula -OR, wherein R is alkyl as defined above, for example C_1-C_5 alkoxy, C_1-C_3 alkoxy, methoxy, n-propoxy, t-butoxy, and the like.

The term "halogen" indicates a member of the seventh main group of the periodical system, i.e. fluoro, chloro, bromo, and iodo; chloro, bromo and iodo being more useful in the present compounds.

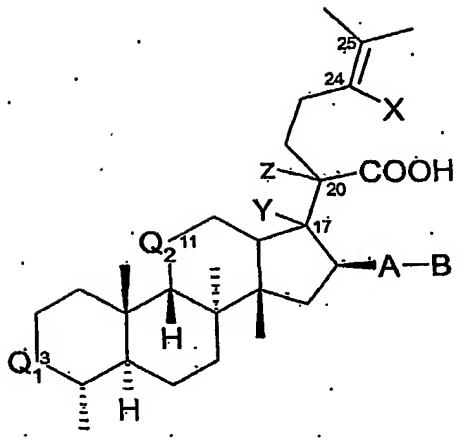
The term "cycloalkylcarbonyl" is intended to indicate a radical of the formula –C(O)-R', wherein R' represents a cyclic alkyl as indicated above.

The term "aryl" is intended to indicate a cyclic, optionally a fused bicyclic, radical, wherein all ring atoms are carbon, and wherein the ring is aromatic, or in the case of a fused ring system, at least one ring is aromatic. Examples of aryl include phenyl, napthyl and tetralinyl.

The expression "easily hydrolysable esters" is used in this specification to denote alkanoyloxyalkyl, aralkanoyloxyalkyl, aroyloxyalkyl, for example acetoxymethyl, pivaloyloxymethyl, benzoyloxymethyl esters and the corresponding 1'-oxyethyl derivatives, or alkoxycarbonyloxyalkyl esters, for example methoxycarbonyloxymethyl esters and ethoxycarbonyloxymethyl esters, and the corresponding 1'-oxyethyl derivatives, or lactonyl esters, for example phthalidyl esters, or dialkylaminoalkyl esters, for example diethylaminoethyl esters. The expression "easily hydrolysable esters" includes *in vivo* hydrolysable esters of the compounds of the invention. Such esters may be prepared using methods known to a skilled person in the art, cf. GB patent No. 1 490 852 hereby incorporated by reference.

<u>Preferred embodiments of compounds of formula I</u>

In a preferred embodiment, the invention relates to compounds of general formula Ia



[Ia]

wherein X represents halogen, trifluoromethyl, cyano, azido, C_{1-6} alkyl, C_{2-6} alkenyl or aryl, wherein said aryl may optionally be substituted by C_{1-6} alkyl, C_{2-6} alkenyl, halogen, azido, trifluoromethyl or cyano;

Y and Z both represent hydrogen, or together with the C-17/C-20 bond form a double bond between C-17 and C-20, or together are methylene and form a cyclopropane ring in combination with C-17 and C-20;

A represents a bond, O, S or S(O);

B represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} acyl, C_{3-7} cycloalkylcarbonyl or benzoyl, all of which are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, C_{1-6} alkoxy and azido, or, if A represents a bond, B may also represent hydrogen;

Q_1 and Q_2 independently represent -C(O)-, -(CHOH)-, -(CHSH)- or -(CW)-, wherein W represents halogen, azido or trifluoromethyl;

and pharmaceutically acceptable salts and easily hydrolysable esters thereof.

In a preferred embodiment of compounds of formula Ia, Y and Z are both hydrogen, and the stereochemical configuration is S at both C-17 and C-20.

In another preferred embodiment of compounds of formula Ia, Y and Z together are methylene and form a cyclopropane ring in combination with C-17 and C-20, and the stereochemical configuration is S at both C-17 and C-20.

In compounds of formula Ia, A is preferably O or S(O).

In compounds of formula Ia, X preferably represents fluoro, chloro, bromo; iodo, cyano, azido or trifluoromethyl.

Q_1 and Q_2 may advantageously be selected from the group consisting of –(CO)- and –(CHOH)-. Q1 may also represent CHF, CHCl, CHBr, CHI, CHN_3.

A still further embodiment of the invention provides compounds of formula Ia, wherein Q_1 and Q_2 both represent –(COH)- group, or one of Q_1 or Q_2 represents -(CO)-, or Q_1 represents CHF, CHCl, CHBr, CHI or CHN_3;
X represents fluoro, chloro, bromo, iodo, trifluorometyl, azido or cyano;
Z and Y together with the C17/C20 bond form a double bond between C-17 and C-20;
A represents oxygen;
B represents C_{1-4} alkyl, optionally substituted with one or more substituents selected from the group consisting of azido, hydroxy, fluoro, chloro and bromo, or B represents a C_{1-4} acyl group or a benzoyl group, both optionally substituted with one or more halogen atoms, such as e.g. fluoro and chloro. Favoured examples of B include ethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 2-azidoethyl, 2-hydroxyethyl, propyl, tert.-butyl, isopropyl, 1,3-difluoro-isopropyl, acetyl, propionyl, chloroacetyl and trifluoroacetyl, and in particular ethyl, 2,2,2-trifluoroethyl, 2-azidoethyl, isopropyl, tert-butyl and acetyl.

When Q_1 and/or Q_2 in formulas I or Ia represent –(COH)-, the stereochemical configuration is preferably 3α and 11α, respectively.

Specific examples of compounds of the invention are
24-Trifluoromethyl fusidic acid sodium salt (Compound 101)
24-Trifluoromethyl fusidic acid pivaloyloxymethyl ester (Compound 102)
24-Chloro-fusidic acid (Compound 103)
24-Chloro-fusidic acid pivaloyloxymethyl ester (Compound 104)
24-Chloro-fusidic acid sodium salt (Compound 105)
24-Trifluoromethyl fusidic acid (Compound 106)
24-Bromo-fusidic acid acetoxymethyl ester (Compound 107)
24-Bromo-fusidic acid (Compound 108)
24-Bromo-fusidic acid sodium salt (Compound 109)
24-Bromo-fusidic acid pivaloyloxymethyl ester (Compound 110)
24-Bromo-16-deacetoxy-16β-thioacetyl-fusidic acid acetoxymethylester (Compound 111)
24-Bromo-16-deacetoxy-16β-isopropylthio-fusidic acid (Compound 112)

24-Bromo-16-deacetoxy-16β-isopropylsulfinyl-fusidic acid (Compound 113) 24-Bromo-16-deacetoxy-16β-thioacetyl-fusidic acid (Compound 114)

24-Bromo-17S,20S-dihydrofusidic acid (Compound 115)

24-Bromo-16-deacetoxy-16β-ethoxy-fusidic acid (Compound 116)

24-Bromo-16-deacetoxy-16β-ethoxy-fusidic acid acetoxymethyl ester (Compound 117)

24-Bromo-16-deacetoxy -16β-(2',2',2'-trifluoroethoxy)-fusidic acid acetoxymethyl ester (Compound 118)

24-Bromo-16-deacetoxy -16β-(2',2',2'-trifluoroethoxy)-fusidic acid (Compound 119)

24-Bromo-17S,20S-fusidic acid acetoxymethyl ester (Compound 120)

24-Bromo-17S,20S-methylene-fusidic acid acetoxymethyl ester (Compound 121)

24-Bromo-17S,20S-methylene-fusidic acid (Compound 122)

3-Deoxy-3β,24-dibromo-fusidic acid (Compound 123)

3α-Azido-24-bromo-3-deoxy-fusidic acid (Compound 124)

24-Iodo-fusidic acid (Compound 125)

24-Iodo-fusidic acid acetoxymethyl ester (Compound 126)

24-Iodo-fusidic acid pivaloyloxymethyl ester (Compound 127)

24-Phenyl-fusidic acid pivaloyloxymethylester (Compound 136)

24-Phenyl-fusidic acid (Compound 137)

24-(4-bromophenyl)-fusidic acid pivaloyloxymethylester (Compound 138)

24-(4-bromophenyl)-fusidic acid (Compound 139)

24-(4-chlorophenyl)-fusidic acid pivaloyloxymethylester (Compound 140)

24-(4-chlorophenyl)-fusidic acid (Compound 141)

24-(3,5-difluorophenyl)-fusidic acid pivaloyloxymethylester (Compound 142)

24-(3,5-difluorophenyl)-fusidic acid (Compound 143)

3-Deoxy-3β,24-Dibromo-fusidic acid acetoxymethyl ester (Compound 144)

The compounds of the invention can be used as such or in the form of salts or easily hydrolysable esters (as defined above). In particular, salts of the present compounds are pharmaceutically acceptable salts, such as alkali metal salts and alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, as well as silver salts and salts with bases, such as ammonia or suitable non-toxic amines, such as lower alkylamines, for example triethylamine, hydroxy-lower alkylamines, for example 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine, cycloalkylamines, for example dicyclohexylamine, or benzylamines, for example N,N'-dibenzylethylenediamine, and dibenzylamine. The silver salts of the compounds may be especially useful for local treatment.

The compounds of the present invention may comprise chiral carbon atom(s) and carbon-carbon double bond(s) which give rise to stereoisomeric forms. The present invention relates to all such isomers, either in pure form or as mixtures thereof. Pure stereoisomeric forms of the compounds of the invention may be obtained by the application of procedures known in the art. Diastereomers may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e. g. liquid chromatography using chiral stationary phases. Said pure stereoisomeric forms may also be derived from the corresponding pure stereoisomeric forms of the appropriate starting materials, provided that the reaction occurs stereoselectively or stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereoselective or stereospecific methods of preparation.

Compounds of the present invention are useful for treating or ameliorating infections in a patient, including a mammalian, and in particular, a human patient. Animals that may be treated with a compound of the invention include, more specifically, domestic animals such as horses, cows, pigs, sheep, poultry, fish, cats, dogs and zoo animals. Compounds of the present invention are particular useful in the treatment of bacterial infections.

Consequently, the present invention provides a method of treating or ameliorating bacterial infections, the method comprising administering to a patient an effective amount of a compound of formula I, optionally together with another therapeutically active compound. Examples of said other therapeutically active compounds include β-lactams, such as penicillins (phenoxymethyl penicillin, benzyl penicillin, dicloxacillin, ampicillin, amoxicillin, pivampicillin, flucloxacillin, piperacillin and mecellinam), cefalosporins (cefalexin, cefalotin, cefepim, cefotaxim, ceftazidim, ceftriazon and cefuroxim), monobactams (aztreonam) and carbapenems (meropenem); macrolides (azithromycin, clarithromycin, erythromycin and

roxithromycin); polymyxins (colistin); tetracyclins (tetracycline, doxycyclin, oxytetracyclin and lymecyclin); aminoglycosides (streptomycin, gentamicin, tobramycin and netilmicin); fluoroquinolones (norfloxacin, ofloxacin, ciprofloxacin and moxifloxacin); clindamycin, lincomycin, teicoplanin, vancomycin, oxazolidones (linezolid), rifamycin and metronidazol. Other compounds which may advantageously be combined with a compound of the invention, especially for topical treatment, include for instance corticosteroids, such as hydrocortisone, betamethasone-17-valerate and triamcinolone acetonid. The compounds may either be administered concomitantly or sequentially.

For use in therapy, compounds of the present invention are typically in the form of a pharmaceutical composition. The invention therefore relates to a pharmaceutical composition comprising a compound of formula I, optionally together with other therapeutically active compounds, together with a pharmaceutically acceptable excipient or vehicle. The excipient must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

Conveniently, the active ingredient comprises from 0.05-99.9% by weight of the formulation.

In the form of a dosage unit, the compound may be administered one or more times a day at appropriate intervals, always depending, however, on the condition of the patient, and in accordance with the prescription made by the medical practitioner. Conveniently, a dosage unit of a formulation contain between 50 mg and 5000 mg, preferably between 200 mg and 1000 mg of a compound of formula I.

In the context of topical treatment it may be more appropriate to refer to "usage unit", which denotes a single dose which is capable of being administered to a patient, and which may be readily handled and packed, remaining as a physically and chemically stable unit dose comprising either the active material as such or a mixture of it with solid or liquid pharmaceutical diluents or carriers.

The term "usage unit" in connection with topical use means a unitary, i.e. a single dose capable of being administered topically to a patient in an application per square centimetre of the infected area of from 0.1 mg to 10 mg and preferably from 0.2 mg to 1 mg of the active ingredient in question.

It is also envisaged that in certain treatment regimes, administration with longer intervals, e.g. every other day, every week, or even with longer intervals may be beneficial.

If the treatment involves administration of another therapeutically active compound it is recommended to consult *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th Ed., J.G. Hardman and L.E. Limbird (Eds.), McGraw-Hill 1995, for useful dosages of said compounds.

The formulations include e.g. those in a form suitable for oral (including sustained or timed release), rectal, parenteral (including subcutaneous, intraperitoneal, intramuscular, intraarticular and intravenous), transdermal, ophthalmic, topical, nasal or buccal administration.

The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy, e.g. as disclosed in Remington, *The Science and Practice of Pharmacy*, 20th ed., 2000. All methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be in the form of discrete units as capsules, sachets, tablets or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid, such as ethanol or glycerol; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. Such oils may be edible oils, such as e.g. cottonseed oil, sesame oil, coconut oil or peanut oil. Suitable dispersing or suspending agents for aqueous suspensions include synthetic or natural gums such as tragacanth, alginate, acacia, dextran, sodium carboxymethylcellulose, gelatin, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, carbomers and polyvinylpyrrolidone. The active ingredients may also be administered in the form of a bolus, electuary or paste.

A tablet may be made by compressing or moulding the active ingredient optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient(s) in a free-flowing form such as a powder or

granules, optionally mixed by a binder, such as e.g. lactose, glucose, starch, gelatine, acacia gum, tragacanth gum, sodium alginate, carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, polyethylene glycol, waxes or the like; a lubricant such as e.g. sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride or the like; a disintegrating agent such as e.g. starch, methylcellulose, agar, bentonite, croscarmellose sodium, sodium starch glycollate, crospovidone or the like or a dispersing agent, such as polysorbate 80. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered active ingredient and suitable carrier moistened with an inert liquid diluent.

Formulations for rectal administration may be in the form of suppositories in which the compound of the present invention is admixed with low melting water soluble or insoluble solids such as cocoa butter, hydrogenated vegetable oils, polyethylene glycol or fatty acids esters of polyethylene glycols, while elixirs may be prepared using myristyl palmitate.

Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active ingredients, which is preferably isotonic with the blood of the recipient, e.g. isotonic saline, isotonic glucose solution or buffer solution. The formulation may be conveniently sterilised by for instance filtration through a bacteria retaining filter, addition of sterilising agent to the formulation, irradiation of the formulation or heating of the formulation. Liposomal formulations as disclosed in *e.g.* Encyclopedia of Pharmaceutical Technology, vol.9, 1994, are also suitable for parenteral administration.

Alternatively, the compound of formula I may be presented as a sterile, solid preparation, *e.g.* a freeze-dried powder, which is readily dissolved in a sterile solvent immediately prior to use.

Transdermal formulations may be in the form of a plaster or a patch.

Formulations suitable ophthalmic administration may be in the form of a sterile aqueous preparation of the active ingredients, which may be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems e.g. as disclosed in Encyclopedia of Pharmaceutical Tehcnology, vol.2, 1989, may also be used to present the active ingredient for ophthalmic administration.

Formulations suitable for topical or ophthalmic administration include liquid or semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops.

Formulations suitable for nasal or buccal administration include powder, self-propelling and spray formulations, such as aerosols and atomisers. Such formulations are disclosed in greater detail in e.g. Modern Pharmaceutics, 2nd ed., G.S. Banker and C.T. Rhodes (Eds.), page 427-432, Marcel Dekker, New York; Modern Pharmaceutics, 3th ed., G.S. Banker and C.T. Rhodes (Eds.), page 618-619 and 718-721, Marcel Dekker, New York and Encyclopedia of Pharmaceutical Technology vol. 10, J Swarbrick and J.C. Boylan (Eds), page 191-221, Marcel Dekker, New York

In addition to the aforementioned ingredients, the formulations of a compound of formula I may include one or more additional ingredients such as diluents, buffers, flavouring agents, colourant, surface active agents, thickeners, preservatives, e.g. methyl hydroxybenzoate (including anti-oxidants), emulsifying agents and the like.

The parenteral formulations are in particular useful in the treatment of conditions in which a quick response to the treatment is desirable. In the continuous therapy of patients suffering from infectious diseases, the tablets or capsules may be the appropriate form of pharmaceutical preparation owing to the prolonged effect obtained when the drug is given orally, in particular in the form of sustained-release tablets.

When the active ingredient is administered in the form of salts with pharmaceutically acceptable non-toxic acids or bases, preferred salts are for instance easily water-soluble or slightly soluble in water, in order to obtain a particular and appropriate rate of absorption.

As suggested above, the composition may contain other therapeutically active components which can appropriately be administered together with the compounds of the invention in the treatment of infectious diseases, such as other suitable antibiotics, in particular such antibiotics which may enhance the activity and/or prevent development of resistance. Corticosteroids may also beneficially be included in the compositions of the present invention. In particular, said other active component may include β-lactams, such as penicillins (phenoxymethyl penicillin, benzyl penicillin, dicloxacillin, ampicillin, amoxicillin, pivampicillin, flucloxacillin, piperacillin and mecellinam), cefalosporins (cefalexin, cefalotin, cefepim, cefotaxim, ceftazidim, ceftriazon and cefuroxim), monobactams (aztreonam) and carbapenems (meropenem); macrolides (azithromycin, clarithromycin, erythromycin and

roxithromycin); polymyxins (colistin); tetracyclins (tetracycline, doxycyclin, oxytetracyclin and lymecyclin); aminoglycosides (streptomycin, gentamicin, tobramycin and netilmicin); fluoroquinolones (norfloxacin, ofloxacin, ciprofloxacin and moxifloxacin); clindamycin, lincomycin, teicoplanin, vancomycin, oxazolidones (linezolid), rifamycin and metronidazol. Other compounds which advantageously may be combined with the compounds of the invention, especially for topical treatments, include e.g. corticosteroids, such as hydrocortisone, betamethason-17-valerate and triamcinolone acetonid.

The treatment of infectious diseases often involves determining whether said disease is resistant or refractory to the treatment, before the treatment is, in fact, initiated. By way of example, samples containing the infectious microbe may be taken from the patient, e.g. blood or urine, after which the sample is cultured and exposed to the treatment to determine whether said infectious organism responds to the treatment. Accordingly, the present invention also provides a method for identifying compounds effective against a microorganism, the method comprising administering a compound of formula I, optionally together with other therapeutically active agents, to a microorganism, and determining whether said compound or mixture of compounds has a toxic or static effect on the microorganism in question.

The compositions of the present invention are not limited to pharmaceuticals, but may also be used in a non-therapeutic context to control microbial growth. By way of example, the selectivity of antimicrobial agents renders them useful to enhance growth of particular microorganisms at the expense of others in a multi-species culture.

Biological activity

In vitro investigations have evidenced high potency of compounds of the invention against strains of both staphylococci and streptococci which are among the most relevant pathogenic bacteria involved in various skin and eye infections. Biological tests have showed equal or in some cases slightly enhanced antibacterial activity against staphylococci of compounds of the invention compared to that of fusidic acid and, more importantly, a significantly improved antibacterial activity against streptococci as appears from Table 1 showing MIC values of selected compounds of formula Ia towards both staphylococci and streptococci.

Compounds.

The fusidic acid analogues of the invention and the reference compounds 201 (fusidic acid (as the sodium salt)), 207, 205 203 and 206 (see notes to Table A) were stored in powder

form at +4°C. When used in assays, they were dissolved in 95% EtOH (3.84 mg/ml) and kept for a maximum of 1 month at -20°C before being discarded.

Bacterial strains used for biological evaluation

Bacterial strain	Origin
Staphylococcus aureus FDA486	Laboratory strain
Staphylococcus aureus CJ12	Laboratory strain
Staphylococcus aureus 8325-4	Laboratory strain
Streptococcus pyogenes DA7121	Clinical isolate from human skin infection
Streptococcus pyogenes DA7864	Clinical isolate from human skin infection

Media.

LB media (per 1000 ml ddH_2O: 10 g Bacto-tryptone, 5 g yeast extract, 10 g NaCl). THB (Todd-Hewitt Broth) media, SIGMA, product number: T1438 (per 1000 ml ddH_2O: 50 g Beef-Heart infusion, 20 g Casein peptone, 2 g Dextrose, 2 g $NaHCO_3$, 2.5 g NaCl, 0.4 g Na_2HPO_4). Plates were made using an agar concentration of 1,5%. Blood-agar plates contained an additional 5% (v/v) defibrinated horse blood purchased from SLU (Swedish Agricultural University), Uppsala.

MIC (minimum inhibitory concentration) determination.

MIC tests on the compounds were done in 96-well micro titer plates (Thermo Labsystems). $4x10^5$ bacteria were inoculated in 0,4 ml growth media (*S. aureus*, LB broth, *S. pyogenes* – TH broth) containing serial dilutions of the compound to be tested starting from 128 µg /ml (dilution factor 2, e.g. 128 µg /ml,64µg /ml, ..., 0.016 µg /ml). The criterion for sensitivity is no visible growth after a 24 h, aerobic incubation at 37°C. Each compound was tested at least twice, and fusidic acid was always included as an experimental control.

Table A

Antibacterial activity measured for selected compounds of the invention. MIC/$\mu g \cdot ml^{-1}$.

Compound no.	*Staph. aureus* FDA486	*Staph. aureus* CJ12	*Staph. aureus* 8325-4	*Strep. pyogenes* DA7121	*Strep. pyogenes* DA7864
108	0.05	0.03	n.t.	0.8	0.8
Ref. comp.201 (Fusidic acid)	0.11	0.03	0.03	3.5	3.5
113	0.22	0.11	n.t.	0.4	0.4
Ref. comp.207	0.22	0.05	n.t.	1.6	1.6
115	0.88	0.06	0.11	1.8	1.8
Ref. comp.205	0.44	0.06	0.11	14	28
116	0.44	0.06	0.11	7	7
Ref. comp.203	0.22	0.06	0.22	7	14
122	0.88	0.22	0.88	7	7
Ref. comp.206	0.22	0.06	0.11	>32	28

Notes to Table A:

Concentration of cells at t=0: $\sim 10^6$/ml. Bacteria grown aerobically in broth at 37°C.

n.t. = not tested

Ref. comp. = reference compound

The reference compounds in Table A are known fusidic acid derivatives. Each reference compound refers to the compound of the invention written above in the same column. The reference compounds are unsubstituted at C-24 and have a double bond between C-24 and C-25. All other structural features of the reference compounds are identical to the corresponding compounds of the invention written above in the same column:

201 Fusidic acid

207 16-Deacetoxy-16β-isopropylsulfinyl-fusidic acid (von Daehne, W. *et al., Adv.Appl.Microbiol.*,1979, vol.25, p. 95-146)

205 17S,20S-Dihydrofusidic acid (Duvold, T. *et al., J. Med. Chem.*, 2001, Vol 44, p. 3125-3131)

203 16-deacetoxy-16β-ethoxy-fusidic acid (von Daehne, W. *et al., Adv.Appl.Microbiol.*,1979, vol.25, p. 95-146)

206 17S,20S-methylene-fusidic acid (Duvold T., *et al., Bioorg. Med. Chem. Lett.*, 2002, Vol. 12, p. 3569-3572)

The above data clearly show that substitution of fusidic acid at position 24 gives rise to a significant increase in the activity against streptococci (2-15 fold) while the activity against staphylococci is essentially retained.

Abbreviations

The following standard abbreviations are used throughout this disclosure:

AcOH = acetic acid

Ac_2O = acetic anhydride

AcOM = acetoxymethylester

Ac = acetyl

aq. = aqueous

Bu = n-butyl

^{t}Bu, tBu = tert-butyl

Comp. = Compound

DBU =1,8-diazabicyclo[5.4.0]undec-7-ene

DMF = dimethylformamide

eq. = equivalent

Et = ethyl

Ether = diethyl ether

EtOAc = ethyl acetate

EtOH = ethanol

Ex. = Example

FA = fusidic acid or fusidic acid analogue ring-A,B,C,D substructure

FCC = Flash Column Chromatography

Fu = fusidic acid ring-A,B,C,D substructure

HMPA = Hexamethyl phosphoric acid triamide

HPLC = High Performance Liquid Chromatography

iPr = isopropyl

Me = methyl

MeOH = methanol

m.p. = melting point

MRSA = meticilline resistant Staphylococcus aureus

Pet.ether = petroleum ether

Ph = phenyl

Phenac = phenacylester

PivOM = pivaloyloxymethylester

Prep. = Preparation

THF = tetrahydrofuran

TLC = Thin Layer Chromatography

rt = room temperature

sat.NaCl = saturated aqueous sodium chloride solution

TMS = trimethylsilyl

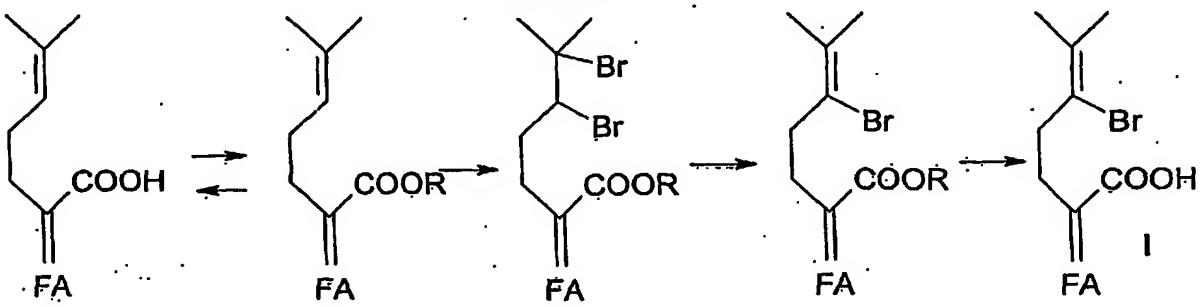
Preparation of the compounds of the invention

The compounds of formula I may be synthesized from known starting materials by different synthetic routes, depending on the requirements presented by each individual compound I, as to availability of starting material, temporary protection of sensitive substituents, purity and yield in the synthetic steps, selection of the preferred order of these steps, and so on.

Illustrative, but non-limiting, examples of the synthesis of different compounds of formula I are given in the following, and the methods of synthesis can also be combined with one another, as judged convenient by the specialist, to furnish the desired compounds of formula I with the proper substitution in ring A, C and D, in the 24-position in the side chain and as the free acids or as salts or as easily hydrolysable esters.

Synthesis of 24-bromo compounds of formula I with FA (fusidic acid/fusidic acid analogue) ring-A,B,C,D substructures, from starting materials 201 – 206 with the same substructures, as illustrated in Scheme 1:

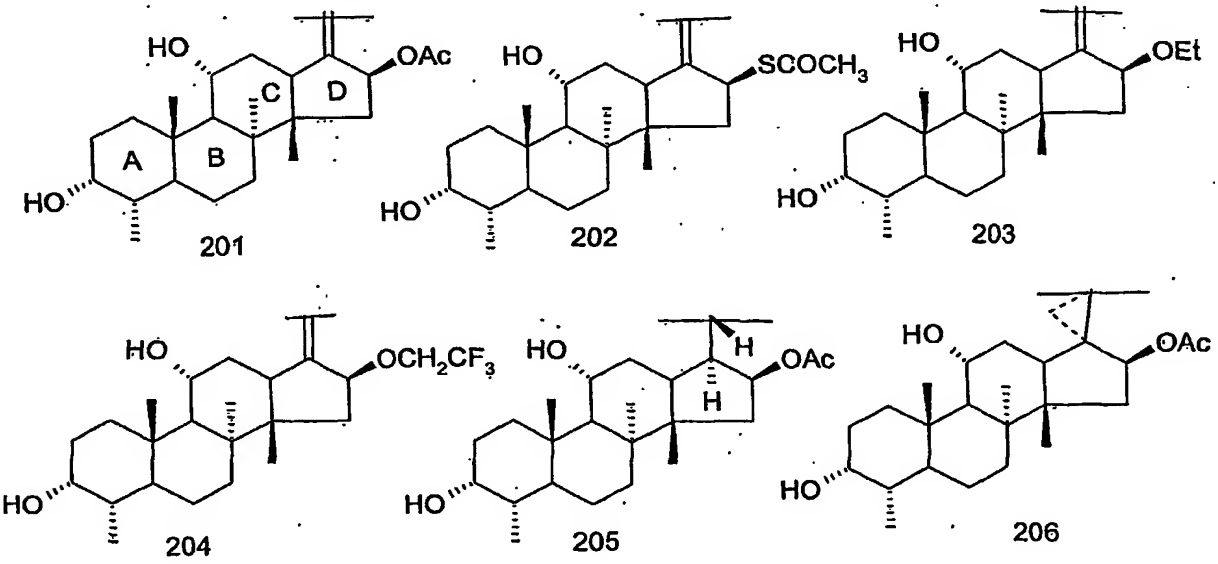
Scheme 1



201	2a	3a	107	108
201	2b	3b	110	108
202	8		111	114
203	9		117	116
204	10		118	119
205	14		120	115
206	15		121	122

Compound 201 = fusidic acid

Exemplified fusidic acid and fusidic acid analogue ring-A,B,C,D substructures, **FA** :

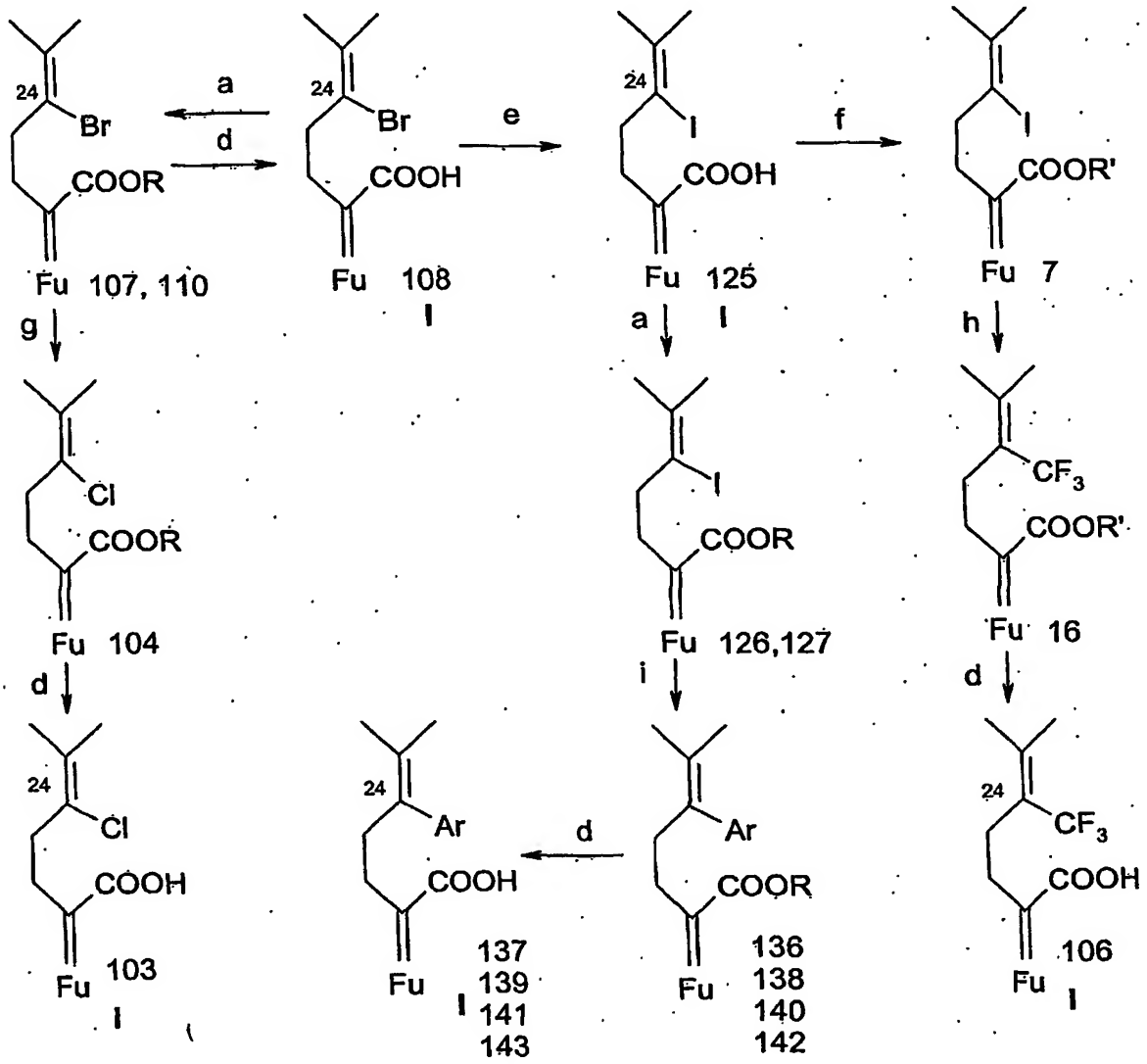


Conditions: (a) $ClCH_2O(CO)R$, Et_3N, DMF (R = Me or $C(CH_3)_3$), rt; (b) Br_2, CCl_4, 0°C; (c) DBU, CCl_4 or CH_3CN, rt; (d) DBU/aq. MeOH or K_2CO_3/MeOH, rt

Fusidic acid or the desired fusidic acid analogue is esterified with chloromethyl acetate or chloromethyl pivalate in a suitable solvent, such as dimethylformamide, in the presence of a suitable base, such as triethylamine. The ester is brominated with bromine in a suitable solvent, such as carbontetrachloride or acetonitrile. The dibromide (a mixture of the 24-diastereoisomers) is de-hydrobrominated by treatment with a suitable base, such as DBU, in a suitable solvent, such as carbontetrachloride or acetonitrile, to give mainly the 24-bromo-fusidic acid- or fusidic acid analogue-ester. If desired, the ester can be used as a prodrug of the corresponding free acid I, having an easily hydrolysable ester group; otherwise the ester is hydrolyzed with a suitable base, such as DBU or K_2CO_3, in a suitable solvent, such as methanol or ethanol, containing water, to give the desired compound I as the free acid.

Conversion of the 24-bromo substituent of a compound I into other 24-substituted compounds I, illustrated by conversion of compound 108; in Scheme 2:

Scheme 2



Conditions: (a) $ClCH_2O(CO)R$, Et_3N, DMF (R = Me or $C(CH_3)_3$), rt; (d) DBU/aq. MeOH or K_2CO_3/MeOH, rt; (e) CuI, KI, HMPA, 120°C; (f) (R'= $-CH_2COPh$) $BrCH_2COPh$, KF, DMF, rt; (g) CuI, LiCl, HMPA, 120°C; (h) CF_3Cu, HMPA, rt; (i) $ArB(OR'')_2$*, $Pd(PPh_3)_4$, K_2CO_3, EtOH+toluene, 90°C. (Fu = fusidic acid ring/A,B,C,D substructure)

* See example 36 – 43 for examples of Ar and $ArB(OR'')_2$

The 24-bromo-fusidic acid- or 24-bromo-fusidic acid analogue-acetoxymethyl ester or

-pivaloyloxymethylester is hydrolyzed to the corresponding free acid by treatment with methanol and aqueous base. The bromo-acid is heated with copper (I) iodide and potassium iodide in HMPA at 120°C, to give the corresponding 24-iodo acid of formula I.

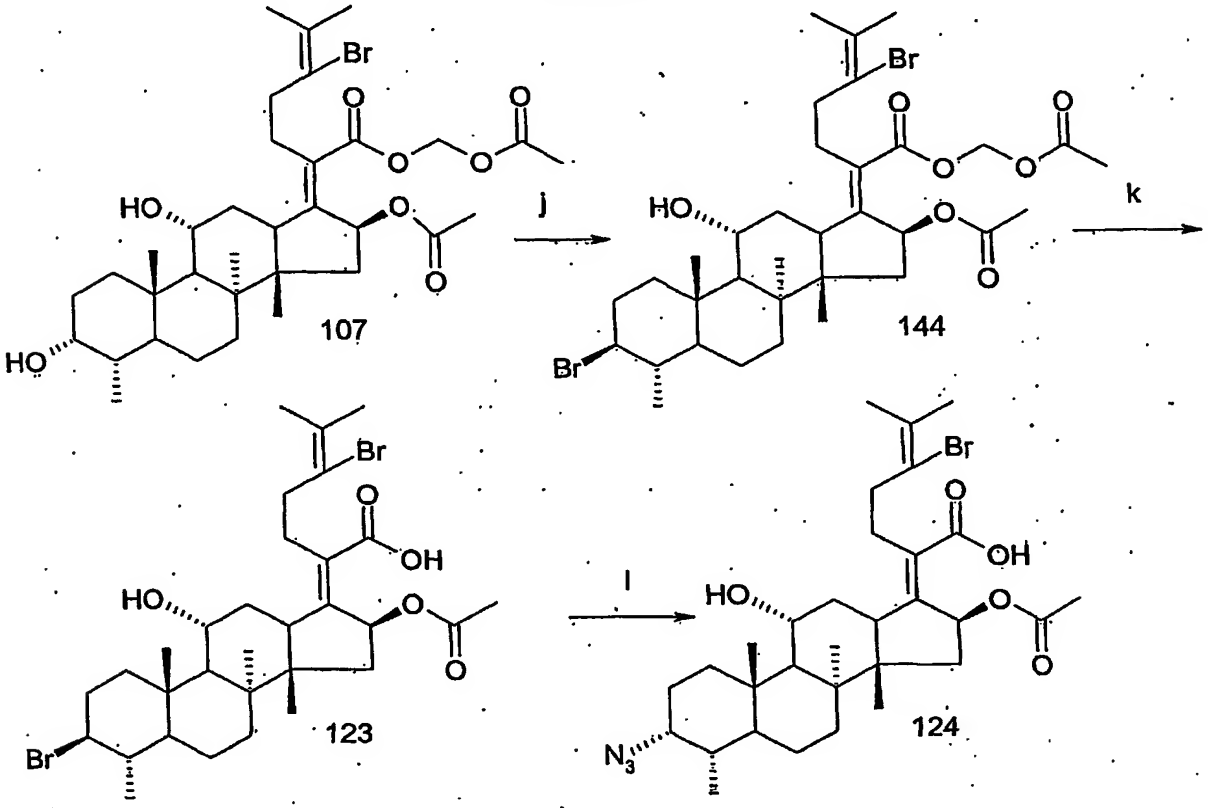
The acid can be esterified to the corresponding phenacyl ester by treatment with phenacylbromide and potassium fluoride in DMF. The phenacyl ester, by reaction with a solution of trifluoromethyl copper in HMPA, gives the corresponding 24-trifluoromethyl ester. The ester may finally be converted to the free 24-trifluoromethyl fusidic acid (or fusidic acid analogue) of formula I by alkaline hydrolysis.

Alternatively, the 24-iodo acid can be esterified to its acetoxymethyl ester or pivaloyloxymethylester as described above, and this can be converted to the corresponding 24-aryl, or alkenyl ester etc., by a suitable coupling reaction, e.g. with a Suzuki-type coupling with an aryl boronic acid, or ester, as shown in Scheme 2. Finally, the corresponding free acid of formula I may be obtained by alkaline hydrolysis of the ester.

In another embodiment the 24-bromo-fusidic acid-, or 24-bromo-fusidic acid analogue-acetoxymethyl ester, or pivaloyloxymethylester, is heated with copper (I) iodide and lithium chloride in HMPA, to give the corresponding 24-chloro ester. This ester gives the free 24-chloro acid of formula I after alkaline hydrolysis.

Synthesis of compounds I, comprising modifications in ring A during the synthetic sequence, illustrated by the synthesis of compounds 123, 124 and 144; in Scheme 3:

Scheme 3



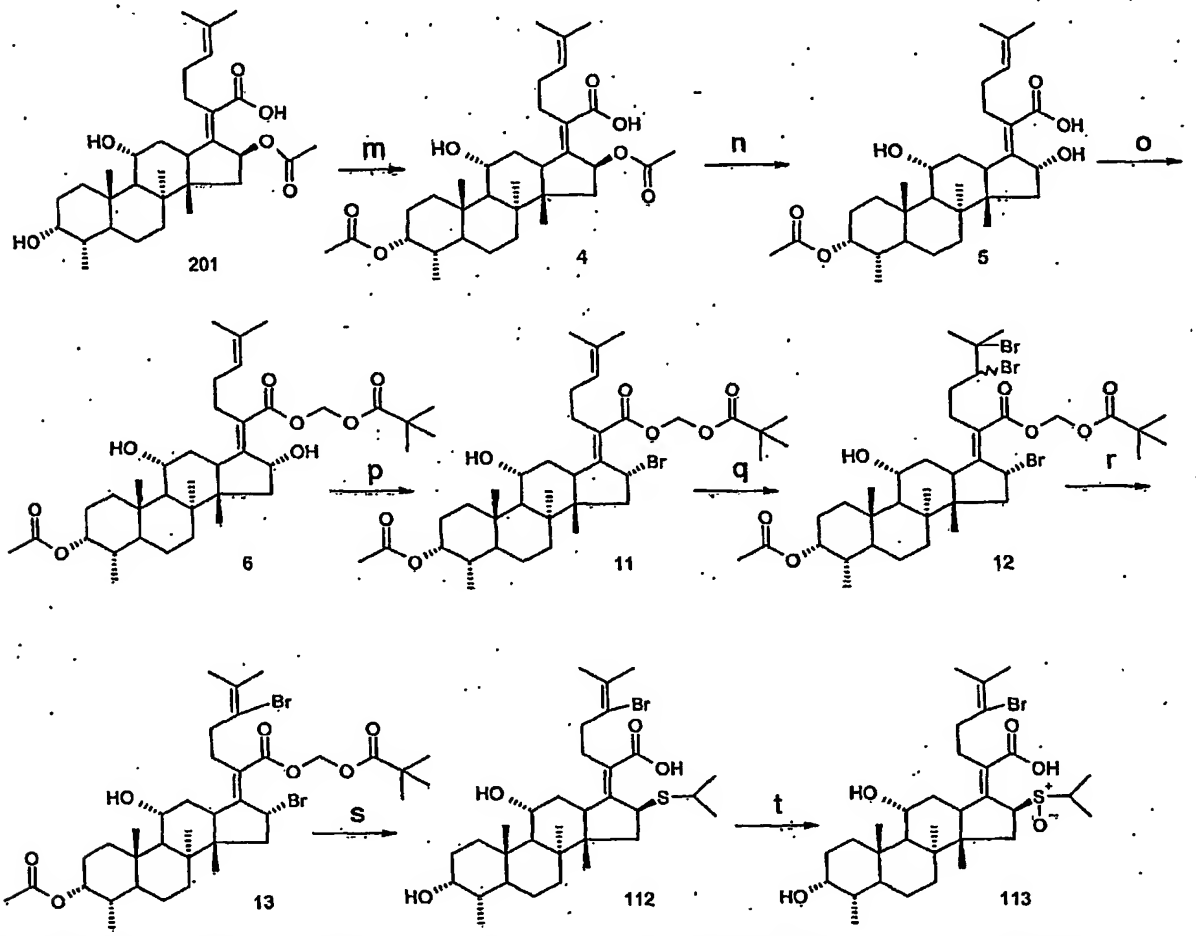
Conditions: (j) Ph_3P, CBr_4, benzene, rt; (k) K_2CO_3, MeOH, rt; (l) LiN_3, DMF, rt

As example of modification of the substitution in one of the rings of the fusidic acid ring-A,B,C,D substructure, after the 24 substituent has been introduced, Scheme 3 shows modifications in ring A:

The 24-bromo-fusidic acid-, or 24-bromo-fusidic acid analogue-acetoxymethyl ester, or -pivaloyloxymethylester, is brominated with triphenylphosphine and tetrabromomethane to give, with inversion of configuration, the corresponding 3-β-bromo ester; the ester can by hydrolyzed to the free acid of formula I. This acid can be further modified, e.g. as shown, by treatment with lithium azide, to give, with another inversion, the corresponding 3-α-azido ester of formula I.

Synthesis of Compounds I, comprising modifications in ring A and ring D during the synthetic sequence, illustrated by the synthesis of compounds 112 and 113; in Scheme 4:

Scheme 4



Conditions: (m) Ac_2O, pyridine, rt; (n) 1. 1 eq. aq. NaOH, MeOH, rt, 2. aq. $NaHCO_3$, 100°C; (o) 1. 1 eq. aq. NaOH, MeOH, rt, 2. $ClCH_2(CO)C(CH_3)_3$, DMF, rt; (p) Cl(CO)OPh, NaBr, DMF, 0°C; (q) Br_2, CCl_4, rt; (r) DBU, CH_3CN, reflux; (s) 1. iPrSH, NaOH, DMF, rt, 2. aq. NaOH, 60°C; (t) 1. 1 eq. aq. NaOH, MeOH, rt, 2. $NaIO_4$, MeOH, rt.

The synthesis of 112 and 113 illustrates a procedure, starting with fusidic acid, in which the 16-substituent in ring D is changed to an alkylthio-, or alkylsulfinyl- group with the correct 16-β-stereochemistry; temporary protection of the 3-hydroxy group and the carboxy group

is applied, and bromine in position 24 is introduced at a proper stage in the synthetic sequence:

Fusidic acid (201) is acetylated at C3 with acetic anhydride and pyridine (4). The sodium salt of 4 is heated with aq. sodium hydrogen carbonate, furnishing the 16-α-hydroxy compound (5) (inversion at C16). The sodium salt of (5) is esterified with chloromethyl pivalate to give (6); this is treated with phenyl chloroformate, dimethylformamide and sodium bromide to give the 16-α-bromo compound (11), i.e. retention at C16. (11) is brominated to the 24,25-dibromo compound (12), and this is dehydrobrominated with DBU to the 24-bromo compound (13). Alkylation of sodium isopropylthiolate with (13) gives the 16-β-isopropylthio intermediate (inversion at C16) which is hydrolyzed with aq. base to the 24-bromo-3-α-hydroxy-16-β-isopropylthio carboxylic acid (112), of formula I. If desired, (112) can be oxidized (with sodium periodate) to give the corresponding sulfoxide (113).

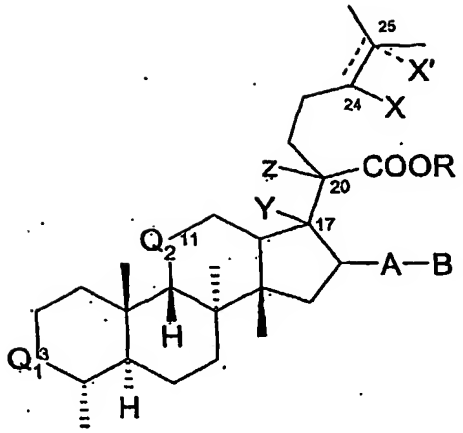
PREPARATIONS AND EXAMPLES

General

All melting points are uncorrected. For ^{1}H (300 MHz) and ^{13}C (75.6 MHz) nuclear magnetic resonance (NMR) spectra chemical shift values (δ) (in ppm) are quoted, unless otherwise specified, for deuteriochloroform solutions relative to internal tetramethylsilane (δ = 0.00) or deuteriochloroform (δ = 76.81 for ^{13}C NMR). The value for a multiplet, either defined (doublet (d), triplet (t), quartet (q)) or not (m) at the approximate mid point is given unless a range is quoted (s = singlet, b = broad). Reaction mixtures were worked up by: extraction with an (indicated) organic solvent, which was shaken with water and/or aq. solutions of (indicated) salts or acids; the organic solution was dried with sodium or magnesium sulfate, and concentrated *in vacuo* on a rotary evaporator. Chromatography was performed on silica gel usually using ethyl acetate and low boiling petroleum ether as eluant. The appropriate fractions were combined and concentrated, in some cases followed by crystallisation or freeze-drying. Solvents: anhydrous solvents were prepared by storing analytical grade solvents over 4Å molecular sieves a few days prior to use. HMPA is classified as a carcinogenic substance and must therefore be handled with the necessary precautions.

Preparation of intermediates for the synthesis of compounds I

The intermediates of the formula I b, below, are listed in table 1:



[Ib]

Table 1

Prep. No.	Comp. No.	Comm. Proced.	Q_1	A-B	Y,Z	R	X,(X')
1	2a	*Prep.1*	>CH-OH (α)	β-O-Ac	Bd	AcOM	H
2	2b	*Prep.2*	>CH-OH (α)	β-O-Ac	Bd	PivOM	H
3	3a	*Prep.3*	>CH-OH (α)	β-O-Ac	Bd	AcOM	Br,Br
4	3b	Prep.3	>CH-OH (α)	β-O-Ac	Bd	PivOM	Br,Br
5	4		>CH-OAc (α)	β-O-Ac	Bd	H	H
6	5		>CH-OAc (α)	α-O-H	Bd	H	H
7	6		>CH-OAc (α)	α-O-H	Bd	PivOM	H
8	8	Prep.1	>CH-OH (α)	β-S-Ac	Bd	AcOM	H
9	9	Prep.1	>CH-OH (α)	β-OEt	Bd	AcOM	H
10	10	Prep.1	>CH-OH (α)	β-OCH_2CF_3	Bd	AcOM	H
11	11		>CH-OAc (α)	α-Br	Bd	PivOM	H
12	12	Prep.3	>CH-OAc (α)	α-Br	Bd	PivOM	Br,Br
13	13		>CH-OAc (α)	α-Br	Bd	PivOM	Br
14	14	Prep.1	>CH-OH (α)	β-O-Ac	H,H	AcOM	H
15	15	Prep.1	>CH-OH (α)	β-O-Ac	$-CH_2-$	AcOM	H
16	7		>CH-OH (α)	β-O-Ac	Bd	Phenac	I
17	16		>CH-OH (α)	β-O-Ac	Bd	Phenac	CF_3

Notes to formula Ib and Table 1;

Prep.	Preparation
Prep.	The procedure is used in other preparations or examples
Comp.	Compound
Comm.Proced.	= Common Procedure
Q_2	>CH-OH (α)
X	As regards those compounds which contain no X' , the configuration around C#24 and C#25 is the same as in formula Ia , i.e. C24 and C25 are connected by a double bond; for those compounds where X = X' = Br , both C24 and C25 are substituted with a bromine atom, and C24 and C25 are connected by a single bond; the compound is a mixture of the two C24 diastereoisomers.
R	H = the free acid Na = the sodium salt AcOM = the acetoxymethyl ester PivOM = the pivaloyloxymethyl ester Phenac = the phenacyl ester
Y,Z	Bd = carbon-carbon bond, i.e. C17 and C20 are connected by a double bond; H,H = 17S-H, 20S-H, i.e. C17 and C20 are connected by a single bond; $-CH_2-$ = [Y,Z]-C17-C20 forms a cyclopropane ring with 17S, 20S-stereochemistry.

PREPARATIONS

Preparation 1: Fusidic acid acetoxymethyl ester (2a)

To a solution of fusidic acid (201) (128.6 g; 250 mmol) in DMF was added Et_3N (45 ml; 33g; 320 mmol) and, after stirring for 30 min at rt, chloromethyl acetate (49 ml; 55g; 500 mmol). The reaction mixture was stirred overnight at rt. and then worked up (EtOAc, water) to give a crude product. This was crystallized from isopropylether to afford pure compound 2a as a white powder, m.p. 103-105°C.

^{13}C NMR, ($CDCl_3$): 170.4, 169.6, 168.4, 150.6, 132.7, 129.3, 122.9, 79.4, 74.4, 71.4, 68.2, 49.2, 48.7, 44.3, 39.5, 39.0, 37.1, 36.2, 36.2, 35.5, 32.4, 30.3, 30.0, 28.8, 28.3, 25.7, 24.2, 22.8, 20.9, 20.8, 20.7 ,17.9, 17.7 ,15.9

Preparation 2: Fusidic acid pivaloyloxymethyl ester (2b)

By following the procedure given for preparation 1 and replacing chloromethyl acetate with chloromethyl pivalate, and performing the reaction at 50°C overnight, fusidic acid pivaloyloxymethyl ester (2b) was obtained as a colourless, amorphous powder.

^{13}C NMR, ($CDCl_3$): 177.0, 170.2, 168.1, 150.9, 132.6, 129.3, 123.0, 79.8, 74.3, 71.4, 68.2, 49.3, 48.8, 44.3, 39.5, 39.0, 38.8, 37.0, 36.3, 36.1, 35.6, 32.3, 30.2, 30.0, 28.8, 28.3, 26.9, 25.7, 24.1, 22.9, 20.8, 17.9, 17.8, 15.9

Preparation 3: 24*R,S*,25-Dibromofusidic acid acetoxymethyl ester (3a)

Fusidic acid acetoxymethyl ester (2a) (6g; 10 mmol) was dissolved in CCl_4 (40 ml) and a solution of bromine (0.56 ml; 1.76g; 11 mmol) in CCl_4 (40 ml) was added during one hour, with stirring and cooling in an ice bath. The resulting, slightly yellow, solution was used in the following step without further purification.

^1H NMR, ($CDCl_3$): 5.91 (m, 1H), 5.78 (bs, 2H), 4.36 (bs, 1H),4.20 (m, 1H), 3.75 (bs, 1H),3.16 (m, 1H),2.80-1.00 (m, 20H), 2.10 (s,3H), 1.97 (bs, 6H), 1.80 (s, 3H), 1.38 (s, 3H), 0.96 (s, 3H), 0.95 (s, 3H), 0.91 (d, 3H)

Preparation 4: 24*R,S*,25-Dibromofusidic acid pivaloyloxymethyl ester (3b)

By following the procedure given for preparation 3 and replacing fusidic acid acetoxymethyl ester (2a) with fusidic acid pivaloyloxymethyl ester (2b), and after concentrating the reaction mixture, purifying the crude product by means of FCC (hexane : EtOAc 50 : 50 as eluant), the title compound 3b was obtained as a colourless foam.

^{13}C NMR, ($CDCl_3$): 177.0, 170.2, 170.2, 167.7, 167.6, 153.0, 153.0, 127.7, 80.1, 80.0, 74.3, 71.4, 68.5, 68.4, 68.2, 68.1, 66.2, 65.8, 60.4, 49.3, 49.2, 48.9, 48.9, 44.5, 39.5, 39.0, 38.8, 37.0, 36.3, 36.1, 35.8, 35.2, 35.1, 32.3, 31.6, 30.2, 30.0, 28.5, 28.2, 28.2, 27.7, 26.9, 24.1, 24.1, 22.8, 22.7, 20.8, 20.8, 18.1, 18.0, 16.0, 14.2

Preparation 5: 3-Acetyl-fusidic acid (4)

To fusidic acid (201) (74.3 g; 0.144 mol) was added pyridine (75 ml; 74 g; 0.93 mol), followed by acetic anhydride (75 ml; 81 g; 0.79 mol), and the mixture was stirred at rt for three hours, after which a clear solution was formed. The product was precipitated by addition of ice and water and recrystallized from methanol/water to give pure compound 4.

^{13}C NMR, ($CDCl_3$):174.5, 171.0, 170.6, 151.1, 132.7, 129.7, 123.0, 74.4, 74.2, 68.3, 49.1, 48.8, 44.3, 39.4, 39.0, 37.8, 37.0, 35.8, 34.8, 32.7, 31.1, 28.7, 28.4, 27.4, 25.7, 24.4, 22.6, 21.3, 20.6, 20.6, 18.1, 17.8, 15.5

Preparation 6: 3- Acetyl-16-deacetoxy-16α-hydroxy fusidic acid (5)

3-Acetoxy-fusidic acid (4) (9.95g; 17.8 mmol) was dissolved in MeOH (250 ml) and neutralized with an equivalent amount of 2N aqueous NaOH (ca. 9 ml). The solvents were evaporated and water (150 ml) was added to the residue. The mixture was heated to reflux and 20 ml of a saturated aqueous solution of $NaHCO_3$ (ca. 1 M) was added during one half hour.

The clear solution was heated to 100°C for eight hours during which an insoluble by-product (the corresponding lactone) was formed. This was removed by filtration, and the filtrate was acidified with 4 N HCl (20 ml) and extracted with EtOAc. The organic phase was extracted with water, dried with $MgSO_4$, and concentrated to give the title compound 5 which was used in the following step without further purification.

^{13}C NMR, ($CDCl_3$): 174.2, 171.2, 164.7, 132.5, 127.6, 123.2, 74.2, 72.2, 68.4, 49.1, 47.4, 43.9, 39.5, 39.2, 37.7, 36.9, 35.9, 34.9, 32.6, 31.0, 29.1, 28.4, 27.3, 25.7, 24.5, 22.7, 21.4, 20.7, 18.4, 17.9, 15.5

Preparation 7: 3-Acetyl-16-deacetoxy-16α-hydroxy fusidic acid pivaloyloxymethyl ester (6)

3-Acetyl-16-deacetoxy-16α-hydroxy fusidic acid (5) (39.7 g; 77 mmol) was dissolved in MeOH (250 ml) and neutralized with 1 eq. of aq. NaOH. The solvent was evaporated and the residue redissolved in DMF (450 ml). Chloromethylpivalate (13.4 ml; 13.9 g; 92 mmol) was added during one half hour with stirring and ice-cooling. The mixture was stirred overnight at rt, after which it was worked up (EtOAc, aq. $CaCl_2$, water, sat.NaCl), dried with $MgSO_4$, and concentrated to give the title compound (6) an oil which was used without further purification in the next step (preparation 11).

^{13}C NMR, ($CDCl_3$): 177.2, 171.0, 168.6, 164.6, 132.6, 127.2, 123.1, 80.0, 74.1, 72.1, 68.4, 49.1, 47.4, 43.7, 39.5, 39.4, 38.8, 37.7, 36.9, 36.0, 34.9, 32.6, 31.0, 28.9, 28.0, 27.4, 26.9, 25.7, 24.5, 22.6, 21.3, 20.7, 18.4, 17.8, 15.5

Preparation 8: 16-deacetoxy-16β-thioacetyl-fusidic acid acetoxymethylester (8)

By following the procedure given for preparation 1 and replacing fusidic acid with 16-deacetoxy-16β-thioacetyl-fusidic acid (202) (von Daehne, W. *et al.*, *Adv.Appl.Microbiol.*,1979, vol.25, p. 95-146), and using 10 eq. each of Et_3N and chloromethyl acetate, and purifying the crude product by FCC with pet.ether : EtOAc 1 : 1 as eluant, the title compound (8) was obtained.

^{13}C NMR, ($CDCl_3$): 194.9, 169.5, 168.4, 151.3, 132.7, 129.5, 122.9, 80.0, 71.4, 68.3, 49.2, 49.0, 45.7, 43.7, 41.4, 39.7, 37.2, 36.3, 35.9, 35.7, 32.7, 30.4, 30.0, 29.9, 29.3, 28.3, 25.7, 24.4, 22.4, 20.7, 20.6, 18.6, 17.7, 16.0

Preparation 9: 16-deacetoxy-16β-ethoxy-fusidic acid acetoxymethylester (9)
By following the procedure given for preparation 1 and replacing fusidic acid with the potassium salt of 16-deacetoxy-16β-ethoxy-fusidic acid (203) (von Daehne, W. *et al.*, *Adv.Appl.Microbiol.*,1979, vol.25, p. 95-146) and using no Et_3N and 10 eq. of chloromethyl acetate, and purifying the crude product by FCC with pet.ether : EtOAc 1 : 1 as eluant, the title compound (9) was obtained.

^{13}C NMR, ($CDCl_3$): 169.7, 169.6, 151.2, 132.4, 128.6, 123.2, 79.6, 78.8, 71.4, 68.4, 65.2, 49.2, 49.0, 43.3, 39.5, 37.0, 36.3, 36.2, 35.8, 35.5, 32.5, 30.2, 30.0, 28.8, 28.2, 25.7, 24.1, 22.8, 20.9, 20.8, 17.8, 17.7, 16.0, 15.3

Preparation 10: 16-deacetoxy-16β-(2',2',2'-trifluoroethoxy)-fusidic acid acetoxymethylester (10)
By following the procedure given for preparation 1 and replacing fusidic acid with 16-deacetoxy-16β-(2',2',2'-trifluoroethoxy)-fusidic acid (204) (von Daehne, W *et al.*, *Adv.Appl.Microbiol.*,1979, vol.25, p. 95-146) and using 10 eq. each of Et_3N and chloromethyl acetate, and purifying the crude product by FCC with pet.ether : EtOAc 1 : 1 as eluant, the title compound (10) was obtained.

^{13}C NMR, ($CDCl_3$): 169.7, 169.1, 151.0, 132.6, 129.9, 123.7, 123.0, 80.1, 79.5, 71.4, 68.3, 67.8, 49.1, 49.0, 43.8, 39.5, 37.1, 36.3, 36.2, 35.8, 35.5, 32.6, 30.3, 30.0, 28.6, 28.2, 25.7, 24.3, 22.7, 20.8, 20.7, 17.7, 17.6, 15.9

Preparation 11: 3-Acetyl-16α-bromo-16-deacetoxy-fusidic acid pivaloyloxymethyl ester (11)
3-Acetyl-16-deacetoxy-16α-hydroxy fusidic acid pivaloyloxymethyl ester (6) (22,8 g; 36.2 mmol) was dissolved in DMF (200 ml) and the solution was stirred in an ice bath under argon. Sodium bromide (18.6 g; 181 mmol) was added and the mixture was stirred for one hour. Phenyl chloroformate (22,8 ml; 28.3g; 181 mmol) was added during one hour at 0°C, followed by stirring for 18 hours at rt. The reaction-mixture was worked up (EtOAc, aq. $CaCl_2$, water, sat.NaCl), dried with $MgSO_4$, and concentrated to give a crude product. This was purified by FCC (10% to 30% EtOAc in pet.ether as eluant) to give the title compound (11) as an oil.

^{13}CNMR,($CDCl_3$): 177.3, 171.0, 167.5, 154.8, 132.6, 129.5, 123.0, 79.8, 74.1, 68.2, 50.6, 49.3, 48.8, 43.5, 42.0, 39.5, 38.9, 37.6, 36.9, 35.8, 35.0, 32.5, 30.9, 28.6, 28.3, 27.3, 27.0, 25.7,24.3,22.8, 21.3, 20.7, 17.8, 17.4, 15.5

Preparation 12: 3-Acetyl-16-deacetoxy-16α-24,25-tribromo fusidic acid pivaloyloxymethyl ester (12)

By following the procedure given for preparation 3 and replacing fusidic acid acetoxymethyl ester (2a) with 3-Acetyl-16α-bromo-16-deacetoxy-fusidic acid pivaloyloxymethyl ester (11), the title compound (12) was obtained as a colourless foam.

^{1}H NMR, ($CDCl_3$): 5.87 (m,2H), 5.64 (bt,1H), 4.93 (bs,1H), 4.35 (bs,1H), 4.14 (dd,1H), 3.46 (bd,1H), 2.80 - 1.00 (m,20H), 2.07 (s,3H), 1.97 (s,3H), 1.84 (s,3H), 1.49 (s,3H), 1.22 (s,9H), 0.98 (s,3H), 0.83 (d,3H), 0.78 (s,3H)

Preparation 13: 3-Acetyl-16-deacetoxy-16α, 24-dibromo fusidic acid pivaloyloxymethyl ester (13)

3-Acetyl-16-deacetoxy-16α-24,25-tribromo fusidic acid pivaloyloxymethyl ester (12) (14.4g; 16.4 mmol) and DBU (7.4 ml; 7.6 g; 49 mmol) in acetonitrile (200 ml) were heated for five hours at 50°C, under argon, with stirring. The reaction mixture was concentrated and worked up (EtOAc, water, sat.NaCl). The crude product was purified by FCC (10% to 15% EtOAc in petr.ether as eluant) to give the title compound (13) as a crystalline product.

^{1}H NMR, ($CDCl_3$): 5.87 (d,1H), 5.84 (d,1H), 5.64 (bt,1H), 4.94 (bs,1H), 4.36 (bs,1H), 3.45 (bd,1H), 2.75 - 2.50 (m,5H), 2.30 - 1.00 (m,15H), 2.07 (s,3H), 1.85 (s,3H), 1.78 (s,3H), 1.46 (s,3H), 1.23 (s,9H), 0.98 (s,3H), 0.83 (dd,3H), 0.77 (s,3H)

Preparation 14: 17S,20S-Dihydrofusidic acid acetoxymethylester (14)

By following the procedure given for preparation 1 and replacing fusidic acid with 17S,20S-Dihydrofusidic acid (205) (Duvold, T. *et al., J. Med. Chem.*, 2001, Vol 44, p. 3125-3131) and using 10 eq. each of Et_3N and chloromethyl acetate, and purifying the crude product by FCC with pet.ether : EtOAc 1 : 1 as eluant, the title compound (14) was obtained.

^{13}C NMR, ($CDCl_3$): 173.8, 170.0, 169.8, 132.4, 123.3, 78.7, 76.5, 71.4, 68.8, 49.3, 45.7, 44.1, 40.6, 38.3, 37.1, 36.3, 34.3, 32.7, 32.5, 30.3, 30.0, 25.7, 25.2, 23.7, 22.8, 21.0, 20.9, 20.7, 17.7, 17.2, 16.0

Preparation 15: 17S,20S-methylene-fusidic acid acetoxymethylester (15)

By following the procedure given for preparation 1 and replacing fusidic acid with 17S,20S-methylene-fusidic acid (206) (Duvold T., *et al.*, *Bioorg. Med. Chem. Lett.*, 2002, Vol. 12, p. 3569-3572) and using 10 eq. each of Et_3N and chloromethyl acetate, and purifying the crude product by FCC with pet.ether : EtOAc 1 : 1 as eluant, the title compound (15) was obtained.

^{13}C NMR, ($CDCl_3$): 171.5, 170.1, 169.6, 132.2, 123.6, 79.1, 78.8, 71.4, 68.3, 49.7, 48.5, 42.6, 40.1, 39.9, 38.6, 37.1, 36.4, 36.3, 36.1, 34.6, 32.3, 31.8, 30.3, 29.9, 26.0, 25.7, 24.1, 22.9, 20.7, 20.7, 18.9, 18.0, 17.6, 16.0

Preparation 16: 24-iodo-fusidic acid phenacylester (7)

Phenacylbromide (0.42g; 2.1 mmol), potassium fluoride (0.27 g; 4.6 mmol) and DMF (10 ml) were stirred for five min. at 90°C under argon. 24-Iodo-fusidic acid (125,) (1.35 g; 2.1mmol) was added, and the mixture was stirred for one hour at 90°C. Work up (ether, water, sat. NaCl, $MgSO_4$) and concentration to gave the title compound (7) as an amorphous powder.

^{13}C NMR, ($CDCl_3$): 171.1, 170.5, 168.6, 152.3, 137.4, 134.3, 133.8, 128.9, 128.2, 127.8, 100.3, 74.4, 71.4, 68.2, 65.8, 60.4, 49.3, 48.9, 44.7, 41.6, 39.5, 39.1, 37.0, 36.4, 36.1, 36.0, 32.2, 31.7, 30.2, 30.0, 28.9, 24.0, 22.9, 21.0, 20.9, 19.4, 18.0, 16.0, 14.2

Preparation 17: 24-trifluoromethyl-fusidic acid phenacylester (16)

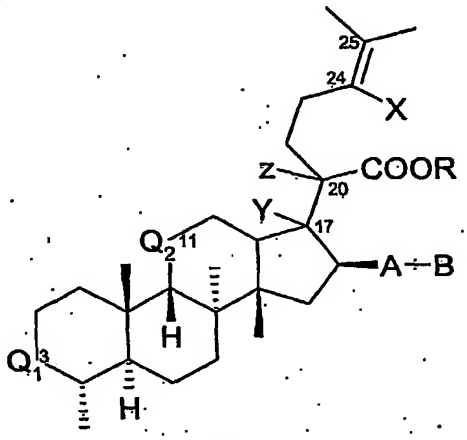
A solution of trifluoromethyl copper complex in HMPA (Kobayashi, Y. *et al.*, *Tetrahedron. Lett.*, 1979, Vol. 42, p. 4071 – 4072), made from trifluoromethyl iodide (0.43 g, 2.2 mmol) and copper powder (0.32 g, 5 mgAt) in HMPA (1.5 ml), was added to 24-iodo-fusidic acid phenacylester (7) (190 mg, 0.25 mmol). The mixture was stirred in a closed vial for 3 days at rt, under argon, then worked up with EtOAc, water and sat.NaCl, dried and concentrated to give a crude product. This was purified by FCC (20% to 40% EtOAc in pet.ether as eluant), followed by preparative HPLC (Lichrospher®-100 RP18, with a gradient of 50% to 0% 0.01 M aq. $NH_4^+HCOO^-$ mixed with 0.01 M $NH_4^+HCOO^-$ in 9:1 acetonitrile : water as eluant). The appropriate fractions were combined, concentrated and extracted with EtOAc; concentration of the EtOAc solution gave the title compound (16) as an oil.

^1H NMR, ($CDCl_3$): 7.88 (dd,2H), 7.58 (t,1H), 7.48 (t,2H), 5.98 (d,1H), 5.48 (d,1H), 5.11 (d,1H), 4.36 (s,1H), 3.75 (bs,1H), 3.10 (bd,1H), 2.75 - 1.00 (m,21H), 2.01 (s,3H), 1.88 (,3H), 1.83 (,3H), 1.38 (s,3H), 0.98 (s,3H), 0.93 (s,3H), 0.92 (d,3H)

EXAMPLES

Compounds I of the invention, of formula Ic

The exemplified compounds I, of formula Ic, below, are listed in table 2:



[Ic]

Table 2

Ex. No.	Comp. No.	Comm. Proced.	Q_1	A-B	Y,Z	R	X
1	101	Ex.9	>CH-OH (α)	O-Ac	Bd	Na	CF_3
2	102	Prep.2	>CH-OH (α)	O-Ac	Bd	PivOM	CF_3
3	103	*Ex.3*	>CH-OH (α)	O-Ac	Bd	H	Cl
4	104		>CH-OH (α)	O-Ac	Bd	PivOM	Cl
5	105	Ex. 9	>CH-OH (α)	O-Ac	Bd	Na	Cl
6	106		>CH-OH (α)	O-Ac	Bd	H	CF_3
7	107	*Ex.7*	>CH-OH (α)	O-Ac	Bd	AcOM	Br
8	108		>CH-OH (α)	O-Ac	Bd	H	Br
9	109	*Ex.9*	>CH-OH (α)	O-Ac	Bd	Na	Br
10	110	Ex.7	>CH-OH (α)	O-Ac	Bd	PivOM	Br
11	111	*Ex.11*	>CH-OH (α)	S-Ac	Bd	AcOM	Br
12	112		>CH-OH (α)	S-iPr	Bd	H	Br
13	113		>CH-OH (α)	SO-iPr	Bd	H	Br
14	114	*Ex.14*	>CH-OH (α)	S-Ac	Bd	H	Br
15	115	Ex.14	>CH-OH (α)	O-Ac	H,H	H	Br
16	116	Ex.14	>CH-OH (α)	O-Et	Bd	H	Br
17	117	Ex.11	>CH-OH (α)	O-Et	Bd	AcOM	Br

Ex. No.	Comp. No.	Comm. Proced.	Q_1	A-B	Y,Z	R	X
18	118	Ex.11	>CH-OH (α)	O-CH_2CF_3	Bd	AcOM	Br
19	119	Ex.14	>CH-OH (α)	O-CH_2CF_3	Bd	H	Br
20	120	Ex.11	>CH-OH (α)	O-Ac	H,H	AcOM	Br
21	121	Ex.11	>CH-OH (α)	O-Ac	-CH_2-	AcOM	Br
22	122	Ex.14	>CH-OH (α)	O-Ac	-CH_2-	H	Br
23	123	Ex.14	>CH-Br (β)	O-Ac	Bd	H	Br
24	124		>CH-N_3 (α)	O-Ac	Bd	H	Br
25	125	*Ex.25*	>CH-OH (α)	O-Ac	Bd	H	I
26	126	Ex.25	>CH-OH (α)	O-Ac	Bd	AcOM	I
27	127		>CH-OH (α)	O-Ac	Bd	PivOM	I
36	136	*Ex.36*	>CH-OH (α)	O-Ac	Bd	PivOM	Ph
37	137	Ex.3	>CH-OH (α)	O-Ac	Bd	H	Ph
38	138	Ex.36	>CH-OH (α)	O-Ac	Bd	PivOM	4-BrPh
39	139	Ex.3	>CH-OH (α)	O-Ac	Bd	H	4-BrPh
40	140	Ex.36	>CH-OH (α)	O-Ac	Bd	PivOM	4-ClPh
41	141	Ex.3	>CH-OH (α)	O-Ac	Bd	H	4-ClPh
42	142	Ex.36	>CH-OH (α)	O-Ac	Bd	PivOM	3,5-F_2Ph
43	143	Ex.3	>CH-OH (α)	O-Ac	Bd	H	3,5-F_2Ph
44	144	Ex.3	>CH-Br(β)	O-Ac	Bd	AcOM	Br

Notes to table 2:

Symbols of Table 2 which are common with those of Table 1, have the same meanings.

Ex. Example

Ex. The procedure is used in other examples

R = AcOM, PivOM: These compounds of formula Ic are easily hydrolysable esters of the corresponding compounds of the invention of formula I (R = H).

Example 1: 24-Trifluoromethyl-fusidic acid sodium salt (Compound 101)
By following the procedure of example 9 and replacing 24-Bromo-fusidic acid (108) with 24-trifluoromethyl fusidic acid (106) the title compound (101) was obtained.

Example 2: 24-Trifluoromethyl-fusidic acid pivaloyloxymethyl ester (Compound 102)
By following the procedure of preparation 2 and replacing fusidic acid with 24-trifluoromethyl fusidic acid (106), and freeze-drying the product, the title compound (102) was obtained.

Example 3: 24-Chloro-fusidic acid (Compound 103)
24-Chloro-fusidic acid pivaloyloxymethyl ester (104) (140 mg, 0.21 mmol) and K_2CO_3 (60 mg, 0.43 mmol) were stirred in MeOH (2 ml) for 3 hours at rt. By FCC of the concentrated reaction mixture, (pet.ether:EtOAc:HCOOH, 90:10:1 to 10:90:1 as eluant), pure title compound 103 was obtained.
^{13}C NMR, ($CDCl_3$): 174.0, 170.6, 152.5, 128.5, 126.8, 74.5, 71.5, 68.2, 49.3, 48.8, 44.6, 39.5, 39.0, 37.0, 36.3, 36.0, 35.6, 32.2, 30.2, 29.9, 27.3, 24.0, 22.9, 21.9, 20.8, 20.6, 20.3, 17.9, 15.9

Example 4: 24-Chloro-fusidic acid pivaloyloxymethyl ester (Compound 104)
24-Bromo-fusidic acid pivaloyloxymethyl ester (10) (283 mg, 0.40 mmol), CuI (240mg, 1.26 mmol), LiCl (30 mg, 0.7 mmol) and HMPA (1.2 ml) were shaken in a closed vial for 3 hours at 120°C. The reaction mixture was worked up (EtOAc and sat.NaCl) to give a crude product. This was purified by FCC with pet.ether: EtOAc (90:10 to 10:90) as eluant to give the pure title compound 104.
^{13}C NMR, ($CDCl_3$): 177.0, 170.2, 167.8, 152.8, 128.5, 128.0, 126.7, 80.0, 74.4, 71.4, 68.2, 49.3, 48.8, 44.6, 39.5, 39.0, 38.8, 37.0, 36.4, 36.0, 35.5, 35.4, 32.2, 30.2, 29.9, 27.2, 26.9, 24.0, 22.9, 21.9, 20.8, 20.4, 17.9, 16.0, 14.2

Example 5: 24-Chloro-fusidic acid sodium salt (Compound 105)
By following the procedure of example 9 and replacing 24-Bromo-fusidic acid (108) with 24-chlorofusidic acid (103), and freeze-drying the product, the title compound (105) was obtained.

Example 6: 24-Trifluoromethyl fusidic acid (Compound 106)

24-trifluoromethyl-fusidic acid phenacylester (17) (15 mg, 0.021 mmol) and sodium thiophenolate (20 mg, 0.15 mmol) in dry DMF (0.5 ml) was stirred under argon at 100°C for five hours. EtOAc (15 ml) was added and the organic solution was extracted with: 3M aq. $CaCl_2$ (10 ml) + 1M aq.H_3PO_4 (0.25 ml), and with (10 ml of each) 3M aq. $CaCl_2$, water and sat.NaCl. After drying and concentration the crude product was purified by FCC, with pet.ether : EtOAc : HCOOH (60 : 40 : ½) as eluant to give, after freeze-drying, the title compound 106 as an amorphous powder.

^{1}H NMR, ($CDCl_3$): 5.87 (d,1H), 4.34 (s,1H), 3.75 (s,1H), 3.06 (bd,1H), 2.70 - 0.80 (m,22H), 1.98 (s,3H), 1.85 (q,3H), 1.83 (q,3H), 1.37 (m,3H), 0.97 (s,3H), 0.91 (s,3H), 0.90 (d,3H)

Example 7: 24-Bromo-fusidic acid acetoxymethyl ester (Compound 107)

24-*R,S*,25-Dibromofusidic acid acetoxymethyl ester (3a) (from 22.3 mmol fusidic acid acetoxymethyl ester) in CCl_4 (280 ml) and DBU (6.64ml; 6.77g; 44.5 mmol) was refluxed for 16 hours. The reaction mixture was filtered from a clay-like precipitate through a cotton wool filter, and the filter was washed with pet.ether and EtOAc, The combined filtrate and washings were concentrated to give the title compound 107 as a crude product (about 70% pure, by NMR) which can be used without further purification in the preparation of compound 108 (Example 8).

A pure sample was obtained by means of FCC (30% to 50% EtOAc in petroleum ether as eluant).

^{13}C NMR, ($CDCl_3$): 170.3, 169.6, 167.9, 152.6, 131.6, 127.9, 120.0,79.5, 74.4, 71.4, 68.2, 49.3, 48.8, 44.6, 39.5, 39.0, 37.8, 37.0, 36.3, 36.0, 35.6, 32.2, 30.2, 29.9, 27.8, 25.3, 24.0, 22.9, 20.8, 20.7, 20.4, 18.0, 16.0

Example 8: 24-Bromo-fusidic acid (Compound 108)

Crude 24-bromo-fusidic acid acetoxymethyl ester (107) or pivaloyloxymethylester (110) (from 44.4 mmol fusidic acid acetoxymethyl ester (2a) or pivaloyloxymethylester (2b)) was dissolved in MeOH (250 ml) and DBU (3 ml) was added to secure a basic reaction. MeOH:water 1:1 (300 ml) was added at rt, during two hours, with stirring which was continued for a further two hours. A 1M KH_2PO_4-solution was added (100 ml) if necessary also phosphoric acid, to give a pH about 4-5; the precipitate which formed was dissolved by extraction, twice, with EtOAc. The organic phase was extracted with water and sat.NaCl, dried with $MgSO_4$, and concentrated to give a crude product. This was purified by FCC (50% EtOAc in pet.ether + 0.5% HCOOH as eluant), followed by recrystallization from EtOAc + toluene (with partial evaporation) to give the pure title compound (108).

^{13}C NMR, ($CDCl_3$): 173.0, 170.5, 152.6, 131.5, 128.1, 120.1, 74.5, 71.4, 68.2, 49.2, 48.8, 44.6, 39.5, 39.0, 37.8, 37.1, 36.2, 36.2, 35.7, 32.4, 30.2, 29.9, 28.0, 25.3, 24.1, 22.8, 20.8, 20.7, 20.4, 18.0, 15.9

Example 9: 24-Bromo-fusidic acid sodium salt (Compound 109)

24-Bromofusidic acid (108) (2,38g; 4.00 mmol) was dissolved in MeOH (30 ml). An equivalent amount of 1N NaOH-solution (4 ml) was added gradually until the pH was about 8.5, as measured with a pH-meter. The resulting solution was concentrated and the residue was dissolved in EtOH (15 ml). EtOAc (25 ml) was added, but crystallization did not take place until the solvents were evaporated, EtOH and EtOAc added and the solvents evaporated once again. The residue now crystallized from EtOH + EtOAc to give the title compound (109) as colourless crystals.

^{13}C NMR, ($CDCl_3$): 179.1, 173.5, 138.8, 138.2, 131.3, 122.6, 76.0, 72.5, 68.9, 50.8, 50.0, 43.8, 40.7, 40.3, 38.5, 38.3, 37.8, 37.5, 36.9, 33.0, 31.1, 31.0, 30.2, 25.4, 23.8, 23.8, 22.5, 21.1, 20.5, 17.9, 16.5

Example 10: 24-Bromo-fusidic acid pivaloyloxymethyl ester (Compound 110)

By following the procedure given Example 7 and replacing 24*R,S*,25-dibromofusidic acid acetoxymethyl ester with 24*R,S*,25-Dibromofusidic acid pivaloyloxymethyl ester (3b) crude title compound (110) was obtained. This can be hydrolyzed, without further purification, to give compound 108. FCC of a sample of the crude product, using 30% to 50% EtOAc in pet.ether as eluant, gave the pure title compound (110) as a light-yellow amorphous foam.

^{13}C NMR, ($CDCl_3$): 177.0, 170.2, 167.8, 152.8, 131.5, 127.9, 120.1, 80.0, 74.4, 71.4, 68.2, 49.3, 48.8, 44.6, 39.5, 39.0, 38.8, 37.7, 37.0, 36.3, 36.0, 35.7, 32.3, 30.2, 30.0, 27.8, 26.9, 25.3, 24.0, 22.9, 20.8, 20.4, 18.0, 16.0

Example 11: 24-Bromo-16-deacetoxy-16β-thioacetyl-fusidic acid acetoxymethylester (Compound 111)

A solution of bromine (45 µl; 140 mg; 0.88 mmol) in CCl_4 (5 ml) was added to a solution of 16-deacetoxy-16β-thioacetyl-fusidic acid acetoxymethylester (8) (0.48 g; 0.8 mmol) in CCl_4 (10 ml), during two hours, under argon, with stirring and cooling in an ice bath. Stirring was continued for 15 min. in the ice-bath and for a further 15 min. at rt. DBU (0.66 ml; 0.67 g; 4.4 mmol) was added, and the mixture was boiled under reflux for 12 hours. The reaction mixture was filtered through filter aid and concentrated *in vacuo*. The residue

was purified by FCC, with 0% to 70% EtOAc in petrether as eluant, to give the title compound (111).

^{13}C NMR, ($CDCl_3$): 194.8, 169.5, 168.0, 153.0, 131.7, 128.1, 120.0,79.9, 71.4, 68.2, 49.3, 49.0, 45.9, 43.8, 41.4, 39.7,37.6, 37.2, 36.4, 35.9, 35.8, 32.8, 30.4, 30.1, 29.9,28.3, 25.3, 24.5, 22.4, 20.7, 20.6, 20.4, 18.8, 16.0

Example 12: 24-Bromo-16-deacetoxy-16β-isopropylthio-fusidic acid (Compound 112)
2-Propanethiol (1.4 ml; 1.13 g; 15 mmol) was dissolved in dry DMF (12.5 ml) and sodium hydride (60% dispersion in oil; 0.6 g; ca. 15 mmol) was added, followed by 3-Acetyl-16-deacetoxy-16α, 24-dibromo fusidic acid pivaloyloxymethyl ester (13) (0.45 g; 0.6 mmol), with stirring at rt, and under argon. Stirring was continued for two hours and the reaction mixture was worked up (EtOAc, water, aq. HCl (to ca. pH4), water, sat.NaCl) and concentrated to an oil. This was dissolved in EtOH (20 ml), and 2 N aq. NaOH (10 ml) was added, and the mixture was heated to 60°C for two hours. The hydrolysis-mixture was worked up as above, and the crude product was purified by FCC (10% to 20% EtOAc in petr.ether + 1%AcOH, as eluant) to give the title compound (112).

^{1}H NMR, ($CDCl_3$): 4.30 (m, 1H), 4.15 (m, 1H), 3.75 (m, 1H), 3.10 (m, 1H), 1.82 (s, 3H), 1.75 (s, 3H), 1.35 (s, 3H), 1.24 (d, 3H, J=6 Hz), 1.18 (d, 3H, J=6 Hz), 0.99 (s, 3H), 0.98 (s, 3H), 0.88 (d, 3H, J=6 Hz) ,2.9 – 1.0 (m, 23H)

Example 13: 24-Bromo-16-deacetoxy-16β-isopropylsulfinyl-fusidic acid (Compound 113)
To a solution of 24-Bromo-16-deacetoxy-16β-isopropylthio-fusidic acid (112) (0.29 g; 0.47 mmol) in MeOH (10 ml) was added 2N aq. NaOH (0.5 ml) and sodium periodate (0.23 g; 1.1 mmol) in water (40 ml). The mixture was stirred for one hour at rt, and acidified with aq. HCl to precipitate the acid. This was filtered off, washed with water and recrystallized from EtOAc to give the title compound (113) as crystals, m.p. 166-168°C.

^{13}C NMR, ($CDCl_3$): 173.7, 159.6, 131.3, 125.8, 120.2, 71.5, 68.3, 60.2, 51.8, 49.5, 48.2, 47.5, 39.7, 38.2, 37.2, 36.3, 36.1, 35.6, 32.6, 30.4, 30.0, 28.0 ,26.6, 25.3, 24.6, 22.7, 20.7, 20.4, 18.3, 17.8, 16.0, 13.5

Example 14: 24-Bromo-16-deacetoxy-16β-thioacetyl-fusidic acid (Compound 114)
24-Bromo-16-deacetoxy-16β-thioacetyl-fusidic acid acetoxymethylester (111) (40 mg; 0.059 mmol) was dissolved in MeOH (2.5 ml) and potassium carbonate (17 mg; 0,12 mmol) was added, and the mixture was stirred for three hours (with access to the moisture of the air). Water (10 ml) was added, and the mixture was acidified to ca. pH 4 with aq. HCl by which the acid precipitated. The mixture was worked up with EtOAc, water and sat.NaCl,

dried with Na_2SO_4 and concentrated to give a crude product. This was purified by FCC (0% to 10% MeOH in dichloromethane as eluant) to give the title compound (114).

^{13}C NMR, ($CDCl_3$): 202.7, 175.6, 133.0, 131.6, 120.4, 71.4, 68.0, 54.5, 50.4, 48.5, 40.8, 40.6, 37.1, 37.0, 36.7, 36.0, 35.2, 32.7, 31.7, 30.2, 29.9, 25.3, 23.4, 23.3, 21.0, 20.4, 19.5, 16.0

Example 15: 24-Bromo-17S,20S-dihydrofusidic acid (Compound 115)

By following the procedure given in Example 14 and replacing 24-Bromo-16-deacetoxy-16β-thioacetyl-fusidic acid acetoxymethylester (111) with 24-Bromo-17S,20S-dihydro-fusidic acid acetoxymethyl ester (compound 120), the title compound (115) was obtained.

^{13}C NMR, ($CDCl_3$): 180.7, 170.1, 130.9, 120.5, 76.3, 71.5, 68.8, 49.4, 49.4, 44.9, 44.2, 40.6, 38.3, 37.2, 36.4, 36.2, 35.1, 34.3, 32.5, 31.3, 30.3, 29.9, 25.4, 23.8, 22.8, 21.0, 20.8, 20.3, 17.2, 15.9

Example 16: 24-Bromo-16-deacetoxy-16β-ethoxy-fusidic acid (Compound 116)

By following the procedure given in Example 14 and replacing 24-Bromo-16-deacetoxy-16β-thioacetyl-fusidic acid acetoxymethylester (111) with 24-Bromo-16-deacetoxy-16β-ethoxy-fusidic acid acetoxymethyl ester (compound 117) the title compound (116) was obtained.

^{13}C NMR, ($CDCl_3$): 171.0, 151.7, 132.6, 131.6, 120.2, 80.9 ,71.5, 68.4, 64.8, 49.5, 49.0, 44.2, 39.8, 37.6, 37.2, 36.5, 35.9, 35.9, 35.1, 32.8, 30.4, 30.1, 28.9, 25.3, 24.4, 22.3, 20.6, 20.5, 18.6, 16.0, 14.7

Example 17: 24-Bromo-16-deacetoxy-16β-ethoxy-fusidic acid acetoxymethyl ester (Compound 117)

By following the procedure given in Example 11 and replacing 16-deacetoxy-16β-thioacetyl-fusidic acid acetoxymethylester (8) with 16-deacetoxy-16β-ethoxy-fusidic acid acetoxymethyl ester (9) the title compound (117) was obtained.

^{13}C NMR, ($CDCl_3$): 169.7, 152.8, 131.2, 127.3, 120.4, 79.6, 78.8, 71.4, 68.4, 65.3, 49.2, 49.1, 43.4, 39.5, 37.7, 37.1, 36.3, 36.3, 35.8, 35.5, 32.5, 30.3, 30.0, 27.8, 25.3, 24.2, 22.8, 20.8, 20.9, 20.3, 17.9, 16.0, 15.3

Example 18: 24-Bromo-16-deacetoxy-16β-(2',2',2'-trifluoroethoxy)-fusidic acid acetoxymethyl ester (Compound 118)

By following the procedure given in Example 11 and replacing 16-deacetoxy-16β-thioacetyl-fusidic acid acetoxymethylester (8) with 16-deacetoxy-16β-(2',2',2'-trifluoroethoxy)-fusidic acid acetoxymethyl ester (10) the title compound (118) was obtained.

^{13}C NMR, ($CDCl_3$): 169.6, 168.7, 152.6, 131.4, 128.5, 123.8, 120.2, 80.1, 79.4, 71.4, 68.2, 67.8, 67.6, 49.1, 49.1, 44.0, 39.5, 37.6, 37.1, 36.2, 35.8, 35.6, 32.5, 30.3, 30.0, 27.6, 25.3, 24.2, 22.8, 20.7, 20.8, 20.3, 17.7, 16.0

Example 19: 24-Bromo-16-deacetoxy-16β-(2',2',2'-trifluoroethoxy)-fusidic acid (Compound 119)

By following the procedure given in Example 14 and replacing 24-Bromo-16-deacetoxy-16β-thioacetyl-fusidic acid acetoxymethylester (111) with 24-Bromo-16-deacetoxy-16β-(2',2',2'-trifluoroethoxy) fusidic acid acetoxymethyl ester (118) the title compound (119) was obtained.

^{13}C NMR, ($CDCl_3$): 175.3, 151.9, 131.4, 129.0, 123.6, 120.2, 80.5, 77.2, 71.5, 68.3, 67.8, 49.1, 49.0, 43.9, 39.6, 37.7, 37.1, 36.2, 35.8, 35.6, 32.5, 30.3, 30.0, 28.0, 25.3, 24.2, 22.8, 20.8, 20.2, 17.7, 16.0

Example 20: 24-Bromo-17S,20S-dihydro-fusidic acid acetoxymethyl ester (Compound 120)

By following the procedure given in Example 11 and replacing 16-deacetoxy-16β-thioacetyl-fusidic acid acetoxymethylester (8) with 17S,20S-dihydro-fusidic acid acetoxymethyl ester (14) the title compound (120) was obtained.

^{13}C NMR, ($CDCl_3$): 173.6, 169.9, 169.7, 130.8, 120.4, 78.8, 76.5, 71.4, 68.8, 49.4, 49.3, 45.4, 43.9, 40.6, 40.6, 38.3, 37.2, 36.4, 36.2, 35.0, 34.2, 32.6, 31.2, 30.4, 30.0, 25.3, 23.8, 22.7, 20.9, 20.9, 20.7, 20.3, 17.2, 16.0

Example 21: 24-Bromo-17S,20S-methylene-fusidic acid acetoxymethyl ester (Compound 121)

By following the procedure given in Example 11 and replacing 16-deacetoxy-16β-thioacetyl-fusidic acid acetoxymethylester (8) with 17S,20S-methylene-fusidic acid acetoxymethyl ester (15) the title compound (121) was obtained.

^{13}C NMR, ($CDCl_3$): 171.5, 169.9, 169.6, 130.9, 120.9, 79.2, 79.0, 71.4, 68.3, 49.6, 48.5, 43.3, 40.4, 39.9, 39.2, 37.1, 36.3, 36.2, 35.9, 35.7, 34.6, 32.4, 30.3, 30.0, 29.5, 25.4, 24.2, 22.8, 21.1, 20.9, 20.7, 20.2, 19.4, 17.9, 15.9

Example 22: 24-Bromo-17S,20S-methylene-fusidic acid (Compound 122)

By following the procedure given in Example 14 and replacing 24-bromo-16-deacetoxy-16β-thioacetyl-fusidic acid acetoxymethylester (111) with 24-Bromo-17S,20S-methylene-fusidic acid acetoxymethyl ester (compound 121), the title compound (122) was obtained. (The FCC-eluant was 50% EtOAc in pet.ether + 1% HCOOH).

^{13}C NMR, ($CDCl_3$): 178.3, 170.0, 130.8, 120.9, 79.6, 71.5, 68.3, 49.3, 48.6, 44.5, 40.8, 40.3, 39.8, 37.1, 36.2, 36.1, 35.9, 34.7, 32.5, 30.3, 29.9, 29.0, 25.3, 24.4, 22.7, 21.4, 20.8, 20.4, 20.2, 17.6, 15.9

Example 23: 3-Deoxy-3β,24-Dibromo-fusidic acid (Compound 123)

By following the procedure given in Example 14 and replacing 24-bromo-16-deacetoxy-16β-thioacetyl-fusidic acid acetoxymethylester (111) with 3-deoxy 3β,24-dibromo-fusidic acid acetoxymethyl ester (compound 144), the title compound (123) was obtained. (The FCC-eluant was 10% EtOAc in pet.ether + 1% HCOOH).

^{13}C NMR, ($CDCl_3$): 173.8, 170.4, 153.0, 131.7, 128.2, 120.0, 74.4, 68.2, 62.7, 49.0, 48.8, 45.5, 44.5, 41.3, 39.4, 39.0, 37.7, 37.2, 36.8, 36.1, 35.1, 32.5, 27.9, 25.4, 23.9, 23.8, 22.0, 20.6, 20.4, 18.9, 17.9

Example 24: 3α-Azido-24-Bromo-3-deoxy-fusidic acid (Compound 124)

3-Deoxy-3β,24-Dibromo-fusidic acid (123) (100 mg; 0.15 mmol) was dissolved in DMF (2.5 ml) and lithium azide (30 mg; 0.6 mmol) was added. The mixture was stirred at rt under argon for 11 days. EtOAc and water (5 ml of each) was added, together with AcOH to give a slightly acidic pH. Work-up (EtOAc, water, sat.NaCl), drying with Na_2SO_4 and concentration gave a crude product which was purified by FCC (Eluant: 0% to 50% EtOAc in pet.ether + 1% HCOOH) to give the title compound (124).

^{13}C NMR, ($CDCl_3$): 174.1, 170.5, 153.1, 131.6, 128.2, 120.0, 74.5, 68.1, 65.4, 49.1, 48.8, 44.6, 39.4, 39.0, 37.8, 37.4, 36.9, 35.9, 35.5, 32.4, 30.8, 27.9, 26.9, 25.4, 24.2, 23.0, 20.6, 20.5, 20.4, 18.1, 16.7

Example 25: 24-Iodo-fusidic acid (Compound 125)

24-Bromofusidic acid (108) (17.0g; 28.5 mmol), CuI (27.2g; 143 mmol), KI (43.4g; 285 mmol) and HMPA (100 ml) was heated in an oil-bath a for 20 hours at 120°C, under argon, with stirring and with a reflux condenser. Water (400 ml) was added, and the resulting viscous mixture was extracted four times with EtOAc (400ml in total). The organic phase was filtered through filter aid, which was washed with EtOAc. The combined organic phase was extracted with 20% aqueous $Na_2S_2O_5$, twice with water, and with sat.NaCl. After drying

with $MgSO_4$ the solvent was evaporated, and the residue was stirred with toluene (300 ml) for three hours. The precipitate was isolated by filtration, washed with toluene and pet.ether and dried to give almost pure title compound 125 as beige-coloured crystals.

^{13}C NMR, ($CDCl_3$): 173.8, 170.6, 152.3, 137.4, 128.0, 99.9, 74.5, 71.5, 68.2, 60.4, 49.3, 48.8, 44.5, 41.7, 39.5, 39.0, 37.0, 36.4, 36.0, 32.1, 31.6, 30.2, 29.9, 24.0, 23.0, 20.9, 20.7, 19.5, 17.9, 15.9, 14.2

Example 26: 24-Iodo-fusidic acid acetoxymethyl ester (Compound 126)

By following the procedure given for example 25 and replacing compound 108 with 24-bromofusidic acid acetoxymethyl ester (107), crude compound 126 was obtained. This was purified by FCC, with 40% EtOAc in pet.ether as eluant, to give the title compound 126 as an amorphous substance.

^{13}C NMR, ($CDCl_3$): 170.3, 169.6, 168.0, 152.5, 137.5, 127.6, 99.8, 79.5, 74.4, 71.4, 68.1, 49.4, 48.8, 44.6, 41.7, 39.5, 39.0, 36.9, 36.5, 35.8, 32.0, 31.6, 30.1, 29.9, 28.6, 23.9, 23.1, 20.9, 20.8, 20.8, 19.4, 17.9, 16.0, 14.2

Example 27: 24-Iodo-fusidic acid pivaloyloxymethyl ester (Compound 127)

24-Iodo-fusidic acid (125) (0.84g; 1.31 mmol) and triethylamine (0.19ml; 0,14g; 1.35 mmol) was dissolved in DMF (5ml) and stirred for 20 min. at rt. Chloromethyl pivalate (0.30ml; 0,32g; 2.1 mmol) was added and the mixture stirred overnight at rt. The reaction mixture was worked up by extraction with 3M aqueous $CaCl_2$, water and sat.NaCl, dried with $MgSO_4$ and concentrated. The residue was purified by FCC, with 40% EtOAc in pet.ether as eluant, to give the title compound 127 as an amorphous substance .

^{13}C NMR, ($CDCl_3$): 177.0, 170.2, 167.8, 152.8, 137.5, 127.7, 99.7, 80.1, 74.4, 71.4, 68.2, 60.4, 49.3, 48.8, 44.6 ,41.6, 39.5, 39.0, 38.8, 37.1, 36.3, 36.1, 36.0, 32.3, 31.6, 30.2, 30.0, 28.6, 26.9, 24.1, 22.8, 20.8, 20.8, 19.5, 18.0, 16.0, 14.2

Example 28: Cream

24-Bromo-fusidic acid sodium salt	1 g
Petrolatum	7.5 g
Liquid paraffin	7.5 g
Spermaceti	2.5 g
Sorbitane monopalmitate	2.5 g
Polyoxyethylene sorbitane monopalmitate	2.5 g

Water	26.5 g
	50 g

Heat petrolatum, paraffin, spermaceti, sorbitane monopalmitate and polyoxyethylene sorbitane monopalmitate to 70°C and slowly add water under continuous stirring. Continue stirring until the cream has cooled. Triturate 24-Bromo-fusidic acid sodium salt, into the cream base and homogenise using a roller mill. Fill the cream into aluminium collapsible tubes.

Example 29: Ointment

24-Bromo-fusidic acid sodium salt	1 g
Liquid paraffin	6.9 g
Cetanol	0.2 g
Lanolin anhydrous	2.3 g
Petrolatum	39.6 g
	50 g

Melt paraffin, cetanol, lanolin and petrolatum at 70°C. After cooling to below 40 °C triturate 24-Bromo-fusidic acid sodium salt. Fill the ointment into lacquered collapsible aluminium tubes.

Example 30: Capsules

24-Chloro-fusidic acid sodium salt	25 g
Microcrystalline cellulose	14.5 g
Magnesium stearate	0.5 g
	40 g

Pass the ingredients through a 60 mesh sieve and mix for 10 min. Fill the mixture into hard gelatine capsules using a capsule fill weight of 400 mg.

Example 31: Tablets

24-Bromo-fusidic acid sodium salt	25 g
Avicel™	12 g
STA-Rx 1500	12 g
Magnesium stearate	1 g

	50 g

16-Deacetoxy-16β-(2',2',2'-trifluoroethoxy)-17S,20S-methanofusidic acid, sodium salt, Avicel™ and STA-Rx are mixed together, sieved through a 0.7 mm sieve and thereafter mixed with magnesium stearate: The mixture is pressed into tablets each of 500 mg.

Example 32: Suspension

24-Bromo-16-deacetoxy-16β-isopropylsulfinyl-fusidic acid sodium salt	1 g
Citric acid	0.09 g
Sodium monohydrogenphosphate	0.14 g
Sucrose	5 g
Tween™ 80	0.01 g
Potassium sorbate	0.04 g
Carboxymethylcellulose-Na	0.1 g
Water	qs. to 100 ml suspension.

The crystals are micronized and suspended in a solution of citric acid, sodium monohydrogen phosphate, sucrose, potassium sorbate and Tween™ 80 in 10 ml water, if necessary with slight warming. Carboxymethylcellulose-Na is dissolved in 4 ml boiling water. After cooling, it is added to the other ingredients. The suspension is homogenised in a blender and finally water is added to a total volume of 100 ml.

Example 33: Ointment

A: 24-Bromo-16-deacetoxy -16β-(2',2',2'-trifluoroethoxy)-fusidic acid sodium salt	1 g
B: One of the compounds: hydrocortisone, triamcinolone or fluocinolone	0.5 g
Liquid paraffin	6.9 g
Cetanol	0.2 g
Lanolin anhydrous	2.3 g
Petrolatum	39.1 g
	50 g

Melt paraffin, cetanol, lanolin and petrolatum at 70°C. After cooling to below 40 °C, triturate A and B. Fill the ointment into lacquered collapsible aluminium tubes.

Example 34: Ointment

A: 24-Bromo-17S,20S-dihydrofusidic acid	1.5 g
B: Tetracycline	1.5 g
Liquid paraffin	13.8 g
Cetanol	0.4 g
Lanolin anhydrous	4.6 g
Petrolatum	78.2 g
	100 g

Melt paraffin, cetanol, lanolin and petrolatum at 70°C. After cooling to below 40 °C, triturate A and B. Fill the ointment into lacquered collapsible aluminium tubes.

Example 35: Eye gel

24-Bromo-16-deacetoxy-16β-(2',2',2'-trifluoroethoxy)-fusidic acid	10 g
Benzalkonium chloride	0.1 g
Carbomer	5 g
Mannitol	50 g
Sodium edetate	0.5 g
Sodium hydroxide	q.s.
Sterile water	up to 100 g

Dissolve disodium edetate and mannitol in water for injection in a stainless steel vessel equipped with a stirring tool and a built-in homogenizer. Add Carbomer 934P, evacuate the vessel and autoclave the dispersion under slow stirring and homogenizing at high speed. Cool down to 70 °C, stop agitator and homogenizer. Add 24-Bromo-16-deacetoxy-16β-(2',2',2'-trifluoroethoxy)-fusidic acid, sodium salt micronized, sterile - evacuate the vessel and let the 24-Bromo-16-deacetoxy-16β-(2',2',2'-trifluoroethoxy)-fusidic acid sink during slow agitation. Homogenize at high speed for 10 minutes at 70 °C. Cool down to below 30 °C during stirring and homogenizing at low speed. Add a sterile solution of benzalkonium chloride in water for injection under slow stirring. Neutralise the carbomer 934 P by adding a sterile solution of sodium hydroxide 1.050 kg in water for injection. Stir and homogenize at low speed for 5 minutes. Adjust - if necessary - the pH to 5.4 - 5.8. Transfer the eye gel to storage tanks using nitrogen pressure and the low speed homogenizing transfer system.

Store at room temperature until filling. The eye gel is filled aseptically in sterile tubes using a fill weight of 3.5 g.

Example 36: 24-Phenyl-fusidic acid pivaloyloxymethylester (Compound 136)

Phenylboronic acid (50 mg, 0.4 mmol) and EtOH (0.25 ml) was added to a solution of 24-iodo-fusidic acid pivaloyloxymethylester (127) (150 mg, 0.2 mmol) in toluene (1.5 ml) and argon was bubbled through the mixture for 2 min. K_2CO_3 (2M aq. solution, 0.3 ml) and $Pd(PPh_3)_4$ (11.5 mg, 0.01 mmol) were added, and the mixture was shaken at 90°C for 20 hours under argon. The reaction mixture was worked up with EtOAc, water and sat.NaCl, dried and concentrated. The resulting crude product was purified by FCC (20% EtOAc in pet.ether as eluant) to give the pure title compound 136.

^{13}C NMR, ($CDCl_3$): 177.0, 170.2, 167.7, 152.3, 144.1, 133.9, 129.6, 128.9, 128.4, 127.9, 125.9, 80.0, 74.3, 71.4, 67.9, 48.9, 48.7, 44.4, 39.4, 39.0, 38.8, 36.9, 36.3, 36.1, 35.4, 35.0, 32.2, 30.0, 27.4, 26.9, 23.9, 22.7, 22.0, 20.8, 20.8, 20.0, 17.9, 15.9

Example 37: 24-Phenyl-fusidic acid (Compound 137)

By following the procedure of example 3 and replacing 24-chloro-fusidic acid pivaloyloxymethyl ester (104) with 24-phenyl-fusidic acid pivaloyloxymethylester (136), and inserting an aqueous work up procedure (EtOAc, water + aq. HCl to pH ca. 2 and sat.NaCl) before the FCC, the pure title compound 137 was obtained.

^{13}C NMR, ($CDCl_3$):173.9, 170.6, 151.7, 144.1, 134.0, 129.6, 129.5, 128.4, 127.9, 125.9, 74.4, 71.5, 67.9, 48.9, 48.6, 44.3, 39.4, 39.0, 36.8, 36.3, 36.1, 35.4, 35.0, 32.2, 30.0, 30.0, 27.4, 23.8, 22.8, 22.0, 20.8, 20.7, 20.0, 17.9, 15.9

Example 38: 24-(4-bromophenyl)-fusidic acid pivaloyloxymethylester (Compound 138)

By following the procedure of example 36 and replacing phenylboronic acid with [2-(4-bromophenyl)-5,5-dimethyl-1,3,2-dioxaborinane] the title compound 138 was obtained.

^{13}C NMR, ($CDCl_3$):177.0, 170.2, 167.7, 152.5, 142.9, 132.9, 131.3, 131.1, 129.0, 128.6, 119.9, 80.0, 74.3, 71.4, 68.0, 49.0, 48.6, 44.5, 39.4, 39.0, 38.8, 37.0, 36.2, 35.1, 35.0, 32.4, 30.1, 30.0, 27.4, 26.9, 24.1, 22.7, 22.0, 20.8, 20.7, 20.0, 18.0, 15.9

Example 39: 24-(4-bromophenyl)-fusidic acid (Compound 139)

By following the procedure of example 3 and replacing 24-chloro-fusidic acid pivaloyloxymethyl ester (104) with 24-(4-bromophenyl)-fusidic acid pivaloyloxymethylester (138), and inserting an aqueous work up procedure (EtOAc, water + aq.HCl to pH ca. 2 and sat.NaCl) before the FCC, the pure title compound 139 was obtained.

^{13}C NMR, ($CDCl_3$):174.0, 170.6, 152.1, 142.9, 133.0, 131.3, 131.1, 129.1, 128.4, 119.8, 74.3, 71.5, 68.0, 49.0, 48.6, 44.4, 39.4, 39.0, 37.0, 36.2, 35.1, 35.0, 32.3, 30.1, 30.0, 27.4, 24.0, 22.7, 22.1, 20.8, 20.6, 20.0, 17.9, 15.9

Example 40: 24-(4-chlorophenyl)-fusidic acid pivaloyloxymethylester (Compound 140)
By following the procedure of example 36 and replacing phenylboronic acid with [2-(4-chlorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane] the title compound 140 was obtained.
^{13}C NMR, ($CDCl_3$):177.0, 170.2, 167.8, 152.3, 142.4, 132.9, 131.8, 130.9, 129.1, 128.7, 128.2, 80.0, 74.2, 71.4, 68.0, 49.0, 48.6, 44.5, 39.4, 39.0, 37.0, 36.2, 36.1, 35.1, 35.0, 32.3, 30.1, 30.0, 27.4, 26.9, 24.0, 22.7, 22.0, 21.3, 20.8, 20.8, 20.0, 17.9, 15.9

Example 41: 24-(4-chlorophenyl)-fusidic acid (Compound 141)
By following the procedure of example 3 and replacing 24-chloro-fusidic acid pivaloyloxymethyl ester (104) with 24-(4-chlorophenyl)-fusidic acid pivaloyloxymethylester (140), and inserting an aqueous work up procedure (EtOAc, water + aq.HCl to pH ca. 2 and sat.NaCl) before the FCC, the pure title compound 141 was obtained.
^{13}C NMR, ($CDCl_3$):173.9, 170.6, 151.9, 142.4, 133.0, 131.8, 130.9, 129.2, 129.1, 128.1, 74.3, 71.6, 71.5, 68.0, 49.0, 48.6, 44.4, 39.4, 39.0, 37.0, 36.2, 36.1, 35.0, 32.3, 30.0, 27.4, 24.0, 22.7, 22.1, 21.3, 20.8, 20.6, 20.0, 17.9, 15.9

Example 42: 24-(3,5-difluorophenyl)-fusidic acid pivaloyloxymethylester (Compound 142)
By following the procedure of example 36 and replacing phenylboronic acid with [2-(3,5-difluorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane] the title compound 142 was obtained.
^{13}C NMR, ($CDCl_3$):177.0, 170.2, 167.8, 162.9, 162.7, 152.2, 147.2, 132.3, 130.1, 128.5, 112.2, 112.0, 101.4, 80.1, 74.2, 71.4, 68.1, 49.1, 48.6, 44.5, 39.4, 39.0, 38.8, 37.0, 36.2, 35.3, 34.4, 32.4, 30.2, 30.0, 27.6, 26.9, 24.2, 22.6, 22.1, 20.8, 20.7, 20.2, 18.0, 15.9

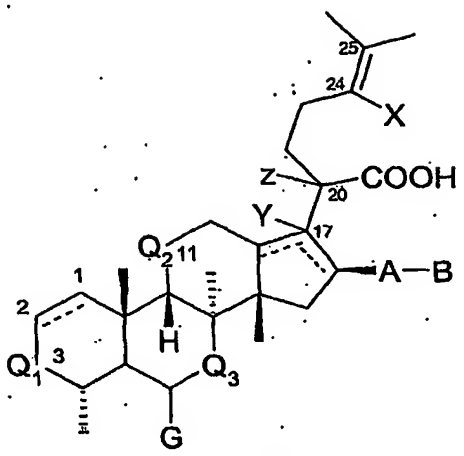
Example 43: 24-(3,5-difluorophenyl)-fusidic acid (Compound 143)
By following the procedure of example 3 and replacing 24-chloro-fusidic acid pivaloyloxymethyl ester (104) with 24-(3,5-difluorophenyl)-fusidic acid pivaloyloxymethylester (142), and inserting an aqueous work up procedure (EtOAc, water + aq.HCl to pH ca. 2 and sat.NaCl) before the FCC, the pure title compound 143 was obtained.

^{13}C NMR, ($CDCl_3$):174.1, 170.6, 162.8, 162.7, 152.0, 147.2, 132.3, 130.2, 129.0, 112.2, 101.4, 74.3, 71.5, 68.1, 49.1, 48.6, 44.4, 39.4, 39.0, 37.0, 36.2, 36.2, 35.3, 34.5, 32.4, 30.2, 29.9, 27.5, 24.1, 22.7, 22.1, 20.7, 20.6, 20.1, 17.9, 15.9

Example 44: 3-Deoxy-3β,24-Dibromo-fusidic acid acetoxymethyl ester (Compound 144)
24-Bromo-fusidic acid acetoxymethyl ester (107) (0.45 g; 0.67 mmol) was dissolved in dry benzene (10 ml) and stirred at rt under argon. Triphenylphosphine (0.7 g; 2.7 mmol) and tetrabromomethane (1.1 g; 3.3 mmol) were added, and the mixture was stirred for one hour at rt. Ether (50 ml) was added, and the precipitated material was removed by filtration. The filtrate was concentrated, and the residue was purified by FCC (eluant: 0% to 50% EtOAc in pet.ether) to give the title compound (144).
^{13}C NMR, ($CDCl_3$): 170.3, 169.6, 167.8, 152.3, 131.8, 128.1, 119.9, 79.5,74.3, 68.1, 62.7, 49.0, 48.8, 45.5, 44.4, 41.3, 39.4,39.0, 37.7, 37.2, 36.8, 36.1, 35.1, 32.5, 27.8, 25.3,23.9, 23.9, 22.0, 20.8, 20.7, 20.4, 18.9, 17.9,

CLAIMS

1. A compound of general formula I



[I]

wherein X represents halogen, trifluoromethyl, cyano, azido, alkyl, alkenyl or aryl, wherein said aryl may optionally be substituted by alkyl, alkenyl, halogen, azido, trifluoromethyl or cyano;

Y and Z both represent hydrogen, or together with the C-17/C-20 bond form a double bond between C-17 and C-20, or together are methylene and form a cyclopropane ring in combination with C-17 and C-20;

A represents a bond, O, S or S(O);

B represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} acyl, C_{3-7} cycloalkylcarbonyl or benzoyl, all of which are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, alkoxy and azido, or, if A represents a bond, B may also represent hydrogen;

Q_1 and Q_2 independently represent $-CH_2-$, -C(O)-, -(CHOH)-, -(CHOR)-, -(CHSH)-, -(NH)-, $-(CHNH_2)-$ or –(CW)-, wherein R represents C_{1-6} alkyl and W represents halogen, cyano, azido or trifluoromethyl;

Q_3 represents $-CH_2-$, -C(O)- or –CHOH-;

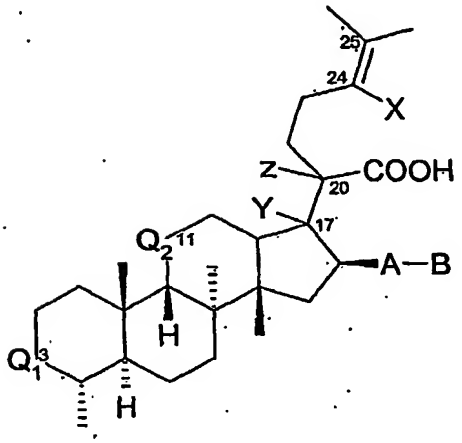
G represents hydrogen, OH or O-CO-CH_3;

two bonds in the pentacyclic ring being depicted with full and dotted lines to indicate that either of the two bonds may be a double bond, in which case Y is absent and Z represents hydrogen;

the bond between C-1 and C-2 being either a single or a double bond;

and pharmaceutically acceptable salts and easily hydrolysable esters thereof.

2. A compound according to claim 1 of formula Ia



[Ia]

wherein X represents halogen, trifluoromethyl, cyano, azido, C_{1-6} alkyl, C_{2-6} alkenyl or aryl, wherein said aryl may optionally be substituted by C_{1-6} alkyl, C_{2-6} alkenyl, halogen, azido, trifluoromethyl or cyano;

Y and Z both represent hydrogen, or together with the C-17/C-20 bond form a double bond between C-17 and C-20, or together are methylene and form a cyclopropane ring in combination with C-17 and C-20;

A represents a bond, O, S or S(O);

B represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} acyl, C_{3-7} cycloalkylcarbonyl or benzoyl, all of which are optionally substituted with one or more substituents selected from amongst halogen, hydroxyl, C_{1-6} alkoxy and azido, or, if A represents a bond, B may also represent hydrogen;

Q_1 and Q_2 independently represent -C(O)-, -(CHOH)-, -(CHSH)- or –(CW)-, wherein W represents halogen, azido or trifluoromethyl;

and pharmaceutically acceptable salts and easily hydrolysable esters thereof.

3. A compound according to any of claims 1 or 2, wherein Y and Z are both hydrogen and wherein the stereochemical configuration is S at both C-17 and C-20.

4. A compound according to any of claims 1 or 2, wherein Y and Z together are methylene and form a cyclopropane ring in combination with C-17 and C-20 and the stereochemical configuration is S at both C-17 and C-20.

5. A compound according to any of claims 1–4, wherein A represents O or S(O).

6. A compound according to any of claims 1–5, wherein X represents fluoro, chloro, bromo, iodo, cyano, azido or trifluoromethyl.

7. A compound according to any of claims 1–6, wherein Q_1 and Q_2 independently represent –C(O)- or –(CHOH)-.

8. A compound according to any of claims 1–6, wherein Q_1 represents CHF, CHCl, CHBr, CHI or CHN_3.

9. A compound according to claim 2, wherein Q_1 and Q_2 both represent a –(CHOH)- group, or one of Q_1 or Q_2 represents -(CO)-, or Q_1 represents CHF, CHCl, CHBr, CHI or CHN3;
X represents chloro, bromo, iodo, trifluorometyl, azido or cyano;
Z and Y together with the C-17/C-20 bond form a double bond between C-17 and C-20;
A represents oxygen;
B represents a C_{1-4} alkyl group, optionally substituted with one or more substituents selected from the list consisting of azido, hydroxy, fluoro, chloro and bromo, or B represents a C_{1-4} acyl group or a benzoyl group, both optionally substituted with one or more halogen atoms.

10. A compound according to claim 9, wherein the halogen atoms with which B is optionally substituted are chloro or bromo.

11. A compound according to claims 9 or 10, wherein B is ethyl, 2,2,2-trifluoro-ethyl, 2,2,2-trichloroethyl, 2-azidoethyl, 2-hydroxyethyl, propyl, tert.-butyl, isopropyl, 1,3-difluoro-isopropyl, acetyl, propionyl, chloroacetyl or trifluoroacetyl.

12. A compound according to claims 1 or 2, wherein Q_1 or Q_2 or both Q_1 and Q_2 represent –(COH)- and the stereochemical configuration is α at both C-3 and C-11.

13. A compound according to claim 1, which is selected from the group consisting of
24-Trifluoromethyl fusidic acid sodium salt (Compound 101)
24-Trifluoromethyl fusidic acid pivaloyloxymethyl ester (Compound 102)
24-Chloro-fusidic acid (Compound 103)
24-Chloro-fusidic acid pivaloyloxymethyl ester (Compound 104)

24-Chloro-fusidic acid sodium salt (Compound 105)
24-Trifluoromethyl fusidic acid (Compound 106)
24-Bromo-fusidic acid acetoxymethyl ester (Compound 107)
24-Bromo-fusidic acid (Compound 108)
24-Bromo-fusidic acid sodium salt (Compound 109)
24-Bromo-fusidic acid pivaloyloxymethyl ester (Compound 110)
24-Bromo-16-deacetoxy-16β-thioacetyl-fusidic acid acetoxymethylester (Compound 111)
24-Bromo-16-deacetoxy-16β-isopropylthio-fusidic acid (Compound 112)
24-Bromo-16-deacetoxy-16β-isopropylsulfinyl-fusidic acid (Compound 113)
24-Bromo-16-deacetoxy-16β-thioacetyl-fusidic acid (Compound 114)
24-Bromo-17S,20S-dihydrofusidic acid (Compound 115)
24-Bromo-16-deacetoxy-16β-ethoxy-fusidic acid (Compound 116)
24-Bromo-16-deacetoxy-16β-ethoxy-fusidic acid acetoxymethyl ester (Compound 117)
24-Bromo-16-deacetoxy -16β-(2',2',2'-trifluoroethoxy)-fusidic acid acetoxymethyl ester (Compound 118)
24-Bromo-16-deacetoxy -16β-(2',2',2'-trifluoroethoxy)-fusidic acid (Compound 119)
24-Bromo-17S,20S-fusidic acid acetoxymethyl ester (Compound 120)
24-Bromo-17S,20S-methylene-fusidic acid acetoxymethyl ester (Compound 121)
24-Bromo-17S,20S-methylene-fusidic acid (Compound 122)
3-Deoxy-3β,24-dibromo-fusidic acid (Compound 123)
3α-Azido-24-bromo-3-deoxy-fusidic acid (Compound 124)
24-Iodo-fusidic acid (Compound 125)
24-Iodo-fusidic acid acetoxymethyl ester (Compound 126)
24-Iodo-fusidic acid pivaloyloxymethyl ester (Compound 127)
24-Phenyl-fusidic acid pivaloyloxymethylester (Compound 136)
24-Phenyl-fusidic acid (Compound 137)
24-(4-bromophenyl)-fusidic acid pivaloyloxymethylester (Compound 138)
24-(4-bromophenyl)-fusidic acid (Compound 139)
24-(4-chlorophenyl)-fusidic acid pivaloyloxymethylester (Compound 140)
24-(4-chlorophenyl)-fusidic acid (Compound 141)
24-(3,5-difluorophenyl)-fusidic acid pivaloyloxymethylester (Compound 142)
24-(3,5-difluorophenyl)-fusidic acid (Compound 143)
3-Deoxy-3β,24-Dibromo-fusidic acid acetoxymethyl ester (Compound 144)

14. A compound according to any of claims 1–13 for use in therapy.

15. A pharmaceutical composition comprising a compound according to any of claims 1-13 together with a pharmaceutically acceptable excipient or vehicle.

16. A pharmaceutical composition according to claim 15 further comprising another therapeutically active compound is selected from the group consisting of antibiotics and corticosteroids.

17. A pharmaceutical composition according to claim 15, wherein said other therapeutically active compound is selected from the group consisting of penicillins (phenoxymethyl penicillin, benzyl penicillin, dicloxacillin, ampicillin, amoxicillin, pivampicillin, flucloxacillin, piperacillin and mecellinam), cefalosporins (cefalexin, cefalotin, cefepim, cefotaxim, ceftazidim, ceftriazon and cefuroxim), monobactams (aztreonam) and carbapenems (meropenem); macrolides (azithromycin, clarithromycin, erythromycin and roxithromycin); polymyxins (colistin); tetracyclins (tetracycline, doxycyclin, oxytetracyclin and lymecyclin); aminoglycosides (streptomycin, gentamicin, tobramycin and netilmicin); fluoroquinolones (norfloxacin, ofloxacin, ciprofloxacin and moxifloxacin); clindamycin, lincomycin, teicoplanin, vancomycin, oxazolidones (linezolid), rifamycin, metronidazol, hydrocortisone, betamethason-17-valerate and triamcinolone acetonid.

18. A method of treating or ameliorating infections in a patient, the method comprising administering to said patient an effective amount of a compound according to any of claims 1-13, and optionally further comprising concomitant or sequential administration of one or more other therapeutically active compounds.

19. A method according to claim 18, wherein said other therapeutically active compound is selected from the group consisting of antibiotics and corticosteroids.

20. A method according to claim 18, wherein said other therapeutically active compound is selected from the group consisting of of penicillins (phenoxymethyl penicillin, benzyl penicillin, dicloxacillin, ampicillin, amoxicillin, pivampicillin, flucloxacillin, piperacillin and mecellinam), cefalosporins (cefalexin, cefalotin, cefepim, cefotaxim, ceftazidim, ceftriazon and cefuroxim), monobactams (aztreonam) and carbapenems (meropenem); macrolides (azithromycin, clarithromycin, erythromycin and roxithromycin); polymyxins (colistin); tetracyclins (tetracycline, doxycyclin, oxytetracyclin and lymecyclin);

aminoglycosides (streptomycin, gentamicin, tobramycin and netilmicin); fluoroquinolones (norfloxacin, ofloxacin, ciprofloxacin and moxifloxacin); clindamycin, lincomycin, teicoplanin, vancomycin, oxazolidones (linezolid), rifamycin, metronidazol, hydrocortisone, betamethason-17-valerate and triamcinolone acetonid.

21. A method according to any of claims 18-20, wherein said infection is a bacterial infection.

22. The use of a compound according to any of claims 1-13 for the manufacture of a medicament for the treatment or amelioration of infections.

23. The use according to claim 22, wherein said medicament further comprises another therapeutically active compound in the same or separate containers adapted for concomitant or sequential administration of said therapeutically active compounds.

24. The use according to claim 23, wherein said other therapeutically active compound is selected from the group consisting of penicillins (phenoxymethyl penicillin, benzyl penicillin, dicloxacillin, ampicillin, amoxicillin, pivampicillin, flucloxacillin, piperacillin and mecellinam), cefalosporins (cefalexin, cefalotin, cefepim, cefotaxim, ceftazidim, ceftriazon and cefuroxim), monobactams (aztreonam) and carbapenems (meropenem); macrolides (azithromycin, clarithromycin, erythromycin and roxithromycin); polymyxins (colistin); tetracyclins (tetracycline, doxycyclin, oxytetracyclin and lymecyclin); aminoglycosides (streptomycin, gentamicin, tobramycin and netilmicin); fluoroquinolones (norfloxacin, ofloxacin, ciprofloxacin and moxifloxacin); clindamycin, lincomycin, teicoplanin, vancomycin, oxazolidones (linezolid), rifamycin, metronidazol, hydrocortisone, betamethason-17-valerate and triamcinolone acetonid.

25. The use according to any of claims 22-24, wherein said infection is a bacterial infection.

Novel Fusidic Acid Derivatives

ABSTRACT

Fusidic acid derivatives substituted at C-24 may be used in therapy for the treatment of infections.